Clinical Study Protocol

A Single Center Study to Evaluate the Effectiveness and Safety of SOTYKTU® (deucravacitinib) in combination with Enstilar® for Moderate to Severe Plaque Psoriasis

Testing Facility

Psoriasis Treatment Center of New Jersey
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Study Sponsor and Principal Investigator

Jerry Bagel, MD

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PROTOCOL SYNOPSIS

Study Title	A Single Center Study to Evaluate the Effectiveness and Safety of Deucravacitinib in combination with Enstilar for Moderate to Severe Plaque Psoriasis
Sponsors	Jerry Bagel, MD
Study Objectives	**Primary Objective:** ●To evaluate the efficacy of combining Deucravacitinib and Enstilar **Secondary Objectives:** ●To evaluate the safety of combining Deucravacitinib and Enstilar. ●To evaluate the subject quality of life when combining Deucravacitinib and Enstilar.
Study Design	30 adult patients with moderate to severe plaque psoriasis will be given Deucravacitinib 6mg QD for the first 8 weeks of the study. At week 8: Subjects who do not meet PASI 25 at week 8 will be discontinued from the study as non-responders. Subjects who achieve ≥PASI 75 at week 8 will remain enrolled and continue Deucravacitinib 6mg QD monotherapy through week 24. Subjects who achieved between PASI 25-74 response will receive 4 weeks of Enstilar (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% applied QD in addition to continuing Deucravacitinib 6mg QD. At week 12, (after 4 consecutive weeks of Enstilar), subjects in the PASI 25-74 group, will discontinue Enstilar QD and continue Deucravacitinib as monotherapy through week 24. Subjects will return at week 28 for safety follow evaluation.
Study Centers	Psoriasis Treatment Center of New Jersey

Study Population	Adult male and female subjects with moderate to severe chronic plaque psoriasis
Main Inclusion Criteria	Subjects must meet the following criteria to be enrolled in this study: 1.Male or female adult ≥ 18 years of age; 2. Diagnosis of chronic plaque-type psoriasis 3. Moderate to severe plaque type psoriasis as defined at baseline by: • BSA affected by plaque-type psoriasis of 10% or greater • PGA score of 3 or greater • PASI ≥ 12. 4. Able and willing to give written informed consent prior to performance of any study-related procedures Must be in general good health (except for disease under study) as judged by the Investigator, based on medical history, physical examination, clinical laboratories, and urinalysis.
Main Exclusion Criteria	Subjects who meet any of the following criteria will be excluded from participation in this study: 1. Other than psoriasis, any clinically significant (as determined by the investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major disease that is uncontrolled. 2. Forms of psoriasis other than chronic plaque-type (e.g., Pustular erythrodermic and/or guttate psoriasis) or drug induced psoriasis 3. Use of oral systemic medications or PUVA phototherapy for the treatment of psoriasis within 4 weeks (includes, but not limited to, oral corticosteroids, methotrexate, acitretin and cyclosporine). 4. Prior use of biologics within the following periods: • Etanercept – 4 weeks • Adalimumab or certolizumab pegol – 8 weeks • IL-17 antagonists – 16 weeks • Ustekinumab or IL-23 pathway inhibitors – 24 weeks • Other biologics - 5 half-lives 5. Patient used topical therapies or UVB phototherapy to treat psoriasis within 2 weeks of the Baseline Visit (includes, but not limited to, topical corticosteroids, vitamin D analogs, or retinoids).

Study Drug Dosage and Administration	All subjects will receive Deucravacitinib 6mg daily at week 0 (baseline) through week 8. At week 8, patients who achieved between PASI 25-74 response will receive 4 weeks of Enstilar (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% once daily in addition to continuing Deucravacitinib 6mg daily. At week 12 (after 4 consecutive weeks of Enstilar therapy), Enstilar will be discontinued and patients will continue Deucravacitinib 6mg daily as monotherapy through week 24. Patients who achieve ≥PASI 75 at week 8 will remain enrolled on Deucravacitinib 6mg QD monotherapy through week 24.
Study Endpoints	Primary Endpoint: Proportion of subjects achieving PASI 75 at week 12 for patients in the Deucravacitinib + Enstilar combination arm. Secondary Endpoints: Proportion of subjects achieving PASI 25-74 at week 8. PASI, PGA, BSA, PGAxBSA and DLQI improvement at weeks 8, 12, 16, 20, 24. PASI 75 at weeks 16 and 24 Serious Adverse Events (SAE's)
Study Duration	*28 weeks*

2 ETHICS AND REGULATORY OBLIGATIONS

2.1 Institutional Review Board (IRB)

Written IRB approval of this protocol must be obtained before the study is initiated. Compliance with Title 21 of the US Code of Federal Regulations (CFR), Part 56, is required in order to protect the rights and welfare of human subjects involved in this study.

2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and its amendments. In addition, the study will be performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.

2.3 Subject Information and Consent

The Informed Consent Form will be reviewed and approved by the IRB. The purpose, duration and possible risks and benefits will be explained to each potential subject. Consent in writing must be obtained from the subject before enrollment into the study. Consents will be signed and dated as required by Title 21 of CFR, Part 50. The consent will also comply with the requirements of the Health Insurance Portability and Accountability Act (HIPAA). The original, signed Informed Consent Form will be retained by the Investigator. A signed copy of the Informed Consent Form will be given to the subject. Each subject will be assigned a subject number that will be used in lieu of the subject's name on further research documentation.

3 INTRODUCTION

3.1 Overview of Psoriasis

Psoriasis is a chronic immunological disease characterized by infiltration of the skin with activated T cells and by abnormal keratinocyte proliferation and differentiation, resulting in marked inflammation and thickening of the epidermis. Psoriasis affects 1-3% of the world population, making it one of the most prevalent inflammatory immunological diseases.[1] There are several clinical subtypes of psoriasis: plaque, guttate, erythrodermic, inverse, and pustular. Plaque psoriasis is the most common type of psoriasis affecting 75-80% of psoriasis sufferers.[2] It presents as raised silvery scale, which can cover large areas, with underlying erythema, itching, and discomfort

3.2 Rationale for Treating Plaque Psoriasis with Deucravacitinib + Enstilar

Deucravacitinib is an investigational TYK2 inhibitor that has been tested for the treatment of moderate-to-severe psoriasis. Combination regimens that utilize a systemic agent with light therapy and/or a topical agent are becoming the standard of care in the United States[3] and Europe[4], confirming the observation of Lebwohl et al[5] in 2004, that the use of two or more therapies to treat patients with moderate to severe psoriasis seems to be the rule rather than the exception. Topical steroids play an in important role in the long-term management of psoriasis and data from the COBRA trial suggests that super potent topical corticosteroids are appropriate and well tolerated for use when added to existing therapeutic regimens i.e. phototherapy, systemic and biologic therapy.[6] In a similarly designed clinical trial using apremilast with Enstilar add- on therapy it was shown that most week-8 partial apremilast responders achieved PASI 75 at week 12 with combination C/BD topical therapy, and maintained PASI 75 through week 16 with apremilast monotherapy.[7] This study is being conducted to determine if adding topical Enstilar to deucravacitinib therapy can help patients who received a partial response at week 8 reach PASI 75 by week 12.

4. STUDY OBJECTIVES

The primary objective of this study is to explore the effectiveness of combining deucravacitinib and Enstilar. Secondary objectives will explore the safety and impact on quality of life for subjects receiving deucravacitinib in combination with Enstilar.

5. INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan

30 subjects affected with plaque psoriasis with body surface area greater than or equal to 10%, and physician's global assessment greater than or equal to 3 and PASI greater than or equal to 12 will receive deucravacitinib 6 mg once daily for 8 weeks.
Subjects who do not achieve at least a PASI 25 at week 8 will be discontinued from treatment and study procedures.

At week 8, subjects who have achieved between a PASI 25-74 will receive Enstilar (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% once daily for 4 weeks in addition to continuing deucravacitinib 6mg daily. These subjects will then discontinue Enstilar at week 12 and remain on deucravacitinib monotherapy through week 24.

Subjects who achieve ≥PASI 75 at week 8 will remain enrolled in the study and continue deucravacitinib QD through week 24. These subjects will not receive Enstilar add-on therapy.

All subjects will be asked to return for a safety follow up visit 4 weeks after the last dose of deucravacitinib.

5.2 Study Population Criteria

Males and females ≥ 18 years of age with moderate-to-severe chronic plaque psoriasis

5.2.1 Inclusion Criteria

Patients who meet all of the following criteria will be enrolled in the study:

1.Male or female adult ≥ 18 years of age

2. Diagnosis of chronic plaque-type psoriasis

3. Moderate to severe plaque type psoriasis as defined at baseline by:
• Physician's Global Assessment (PGA) score of 3 or greater
• Body Surface Area (BSA) affected by plaque-type psoriasis of 10% or greater
• Psoriasis Area Severity Index of 12 or greater

4. Able and willing to give written informed consent prior to performance of any study-related procedures

5. Must be in general good health (except for disease under study) as judged by the Investigator, based on medical history, physical examination, clinical laboratories, and urinalysis. (NOTE: The definition of good health means a subject does not have uncontrolled significant co-morbid conditions).

6.Females of childbearing potential (FCBP) must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline. FCBP who engage in activity in which conception is possible must use one of the approved contraceptive options: hormonal contraception; intrauterine device (IUD); tubal ligation; or partner's vasectomy; Male or female condom diaphragm with spermicide, cervical cap with spermicide, or contraceptive sponge with spermicide.

5.2.2 Exclusion Criteria

Patients will NOT be enrolled in this study if they meet any of the following criteria:

1. Other than psoriasis, any clinically significant (as determined by the Investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major disease that is currently uncontrolled.
2. Pregnant or breast feeding, or considering becoming pregnant during the study.
3. Subjects with a current malignancy or prior malignancy within the last 5 years (excluding successfully treated basal cell carcinoma, squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been adequately treated).
4. Subjects with diagnosis of active tuberculosis or untreated latent tuberculosis. *Subjects will be eligible if they have previously received adequate treatment for latent TB or initiate 4 weeks of prophylactic LTBI treatment prior to*

Baseline visit and agree to complete treatment course as prescribed.

5. History of or positive screening serology for Hepatitis B surface antigen (HBsAg); Hepatitis C virus antibody and/or HIV.
6. Use of any investigational drug within 4 weeks prior to randomization, or within 5 pharmacokinetic/pharmacodynamic half-lives, if known (whichever is longer).
7. Prior treatment with deucravacitinib.
8. Active forms of psoriasis other than chronic plaque-type (e.g., pustular erythrodermic and/or guttate psoriasis) or drug induced psoriasis
9. Prior use of biologics within the following periods:
   • Etanercept – 4 weeks
   • Adalimumab or certolizumab pegol – 8 weeks
   • IL-17 antagonists – 16 weeks
   • Ustekinumab or IL-23 pathway inhibitors – 24 weeks
   • Other biologics - 5 half-lives
10. Use of oral systemic medications or PUVA for the treatment of psoriasis within 4 weeks (includes, but not limited to, oral corticosteroids, methotrexate, acitretin and cyclosporine).
11. Patient used topical therapies within 2 weeks of the Baseline Visit (includes, but not limited to, topical corticosteroids, vitamin D analogs, or retinoids).
12. Patient received UVB phototherapy within 2 weeks of Baseline.
13. Patient has a known hypersensitivity to the excipients of deucravacitinib or Enstilar.
14. Any condition which would place the subject at unacceptable risk if he/she were to participate in the study.

5.3 Source of Subjects and Recruitment Methods

The Investigator will manage the recruitment of subjects upon approval of the study by the Institutional Review Board. Subjects may be recruited from internal patient lists and outside IRB approved advertisements.

5.4 Subject Enrollment and Treatment Assignment

30 subjects of either gender with moderate-to severe plaque psoriasis will receive deucravacitinib 6mg QD for 8 weeks. Participation beyond week 8 will be determinate of subject response according to the study design.

5.5 STUDY TREATMENT

5.5.1 Deucravacitinib Treatment

5.5.2 Deucravacitinib Description

Deucravacitinib is manufactured by Bristol Myers Squibb. Tyrosine kinase 2 (TYK2) is associated with specific cytokine receptors and catalyzes the phosphorylation of signal transducer and activator of transcription (STAT) proteins downstream of these receptors including the receptors for p40-containing cytokines, interleukin (IL)-12, and IL-23, as well as the interferon-α and interferon-β. Type I interferon [IFN]) receptor. TYK2 activity results in the activation of STAT-dependent transcription and functional responses specific for these receptors. Deucravacitinib is a stable deuterium-labeled compound (where deuterium is a stable, nonradioactive isotope of hydrogen) and a potent, highly selective small molecule inhibitor of TYK2. Deucravacitinib has a unique mode of binding that provides the high selectivity over the other members of the JAK family of non-receptor tyrosine kinases.[8] Selective inhibition of TYK2 with the oral agent deucravacitinib at doses of 3 mg daily and higher resulted in greater clearing of psoriasis than did placebo.[9]

5.5.2.1 Deucravacitinib Dosing Schedule

Deucravacitinib 6mg tablets will be supplied by Bristol Myers Squibb and administered once daily (recommended in the mornings). It is recommended the first dose of IP will be taken in the clinic at the baseline visit.

5.5.2.2 Deucravacitinib Dispensing

Subjects will return all unused deucravacitinib tablets to the study site. Site personnel will keep a record of deucravacitinib dispensed to and returned by each subject and note any missed doses.

5.5.2.3 Deucravacitinib Dosage Adjustments

If an SAE or an adverse event that is thought to be related to deucravacitinib and is not alleviated by symptomatic intervention, deucravacitinib will be discontinued.
Subjects who permanently discontinue deucravacitinib therapy under this protocol should receive standard care of psoriasis treatment as prescribed by their physician.

5.5.3 ENSTILAR (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%

5.5.3.1 Enstilar Description

Enstilar foam is a combination of calcipotriene, a vitamin D analog, and betamethasone dipropionate, a corticosteroid, indicated for the topical treatment of plaque psoriasis in patients 18 years of age and older. Each gram of Enstilar Foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone).

5.5.3.2 Enstilar Dosing Schedule

Enstilar will be supplied by LEO Pharma A/S. and applied once daily for 4 weeks for those patients that qualify based on PASI response at week 8.

5.5.3.3 Enstilar Dispensing and Dosing Record

Enstilar will be dispensed to the study subjects by the authorized site personnel following instructions in Enstilar Label. Subjects will return all unused Enstilar to the study site. Site personnel will keep a record of Enstilar dispensed to and returned by each subject and missed doses will be recorded on a subject diary. *See Appendix A*

5.5.3.4 Enstilar Dosage Adjustments

If an SAE or an adverse event that is thought to be related to Enstilar and is not alleviated by symptomatic intervention, Enstilar will be discontinued.

5.5.4 Permitted Concomitant Therapy

The use of steroid-free topical emollients is allowed during the study. Appropriate interventions (e.g., prescribed medications) may be performed as the investigator deems necessary to treat concomitant illnesses and/or safeguard the subjects' wellbeing. No investigational product or device may be used during the study.

5.6 Study Procedures and Assessments

This protocol will consist of a Screening Period (0-30 days), followed by an open-label treatment period of deucravacitinib 6mg QD for 8 weeks. At week 8, subject's PASI scores will be evaluated and subjects who achieve PASI 25-74 will be given add-on Enstilar treatment for 4 weeks (through week 12) followed by deucravacitinib monotherapy through week 24. Subjects who do not achieve PASI 25 at week 8 will be discontinued from the study and follow standard of care from their provider. Subjects who achieve PASI 75 at week 8 will remain on deucravacitinib monotherapy and will not initiate treatment with Enstilar.

5.6.1 Informed Consent

This Study will be conducted in compliance with CFR Title 21, Part 50 (Informed Consent of Human Subjects). Informed consent will be obtained from each subject in writing before participation in the Study. A signed copy of the Informed Consent Form will be provided to each subject. A provision to obtain a signed authorization to provide protected health information to the study sponsor, internal quality assurance agencies, health insurance agencies, and other parties as specified in the Federal Health Insurance Portability and Accountability Act (HIPAA) privacy regulation will be included in the Informed Consent Document. HIPAA authorization is voluntary. However, since the use and release of health information is critical to the conduct of the study, subjects who do not provide authorization to use and disclose their health information will not be enrolled into the study. Subjects who withdraw their authorization to use and release health information during study participation will be formally discontinued from the study. The investigator may use and release at any time all the information collected prior to a subject's withdrawal of the authorization to all authorized parties to satisfy scientific, regulatory, and financial concerns.

5.6.2 Inclusion and Exclusion Criteria

Subjects' eligibility to participate in the study will be determined according to the Inclusion and Exclusion Criteria during the screening period (0 – 30 days prior to the first dose of the study drug). Subjects who ultimately do not satisfy the eligibility criteria except changing treatments and undergoing a washout period, will not be enrolled into the study. Subjects who need to meet eligibility requirements will be asked to make the necessary changes. Subjects who agree and comply will be re-evaluated prior to Baseline.

5.6.3 Demographics and Medical History

The following information will be obtained for each subject during screening: date of birth, sex, race/ ethnic origin, relevant medical and surgical history, including year of diagnosis of plaque psoriasis, and current and previous anti-psoriasis treatments for the last 6 months. All current therapies for other medical conditions will be documented. Medical history will be reviewed and updated at the Baseline Visit to ensure that the patient remains eligible to participate in the study.

5.6.4 Pregnancy Testing

Serum Pregnancy testing (urine β-human chorionic gonadotrophin [β-HCG]) will be conducted in all female subjects, except those without childbearing potential at Screening (-30 to -1). Urine pregnancy tests will be conducted at Baseline (prior to first dose of

deucravacitinib) and at each visit through week 28. An interim urine pregnancy test may be performed if there is reason to believe the subject may have become pregnant during the study. Subjects with a positive pregnancy test will not be eligible to participate or to continue to receive study treatment.

A female of childbearing potential is a sexually mature female who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months). The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization).

5.6.5 Laboratory Testing

Serum chemistry, hematology, fasting lipids, Hepatitis B surface antigen (HBsAg); Hepatitis C virus antibody and HIV and Quantiferon Gold testing will be performed at screening to ensure subject safety prior to baseline. Serum chemistry, hematology and fasting lipids will be performed at weeks 16 and 28.

5.6.6 Physical Examination

A physical examination, including vital signs measurements (blood pressure, pulse and temperature), will be performed according to the schedule of events. The physical examination should include a thorough evaluation of the subject's skin. Any clinically significant abnormalities discovered during physical examinations after the Screening / Baseline visit should be documented and evaluated as potential adverse events.

5.6.7 Physician's Global Assessment (PGA)

PGA will be determined for all subjects throughout the study. PGA is a 6 point scale that records the overall disease severity at each clinical evaluation based on the average degree of erythema, induration, and scaling of areas affected by psoriasis. PGA uses a scale of 0 = Clear, 1 = Minimal, 2 = Mild, 3 = Moderate, 4 = Severe, and 5 = Very Severe. *See Appendix B*

5.6.8 Psoriasis Area Severity Index (PASI)

PASI will be determined for all subjects throughout the study. Four anatomical sites (head, trunk, upper and lower limbs) are assessed for erythema, thickness, and scaling on a scale of 0-4 and degree of skin surface area on a scale of 6. The PASI is a validated instrument that has become standard in clinical trials for psoriasis. The sum of the scores

are then totaled for the PASI score. Psoriasis Area Severity Index scores range from 0 to 72, with higher scores reflecting greater disease severity.[10] *See Appendix C*

5.6.9 Body Surface Area (BSA)

BSA will be determined for all subjects throughout the study. The subjects palm will be selected for the measuring unit of body surface area. The physician will equate the number of palms affected by psoriasis to derive the BSA total.

5.6.10 Patient Reported Outcomes

Subjects will complete the PRO's based on the schedule of assessments. Questionnaires should be prior to medical procedures and clinical evaluations.

Dermatology Life Quality Index (DLQI)[11] to assess symptoms and impacts of dermatologic diseases on quality of life. *See Appendix D*

5.6.11 Photography

Investigator will choose target lesion representative of subject's psoriatic disease at baseline which will be photographed according to the scheduled of assessments. Patients who do not wish to participate in clinical photography may opt out in the informed consent.

5.6.12 Early Discontinuation Procedures

Subjects will be prematurely discontinued from the study under the following conditions:

1. Subject does not reach PASI 25 or greater at week 8
2. Subject requests to withdraw from the study.
3. Subject is noncompliant with protocol schedule, restrictions, and/or requirements as deemed per investigator.
4. Subject experiences an adverse event that makes it difficult or intolerable for the subject to continue treatment, or increases risk to the subject, or interferes with the investigator's ability to clinically evaluate the progress of the subject's treatment.
5. Subject begins an unapproved concomitant therapy for psoriasis or another medical condition that may increase risk to the subject if continuing study treatment.
6. Subject cannot be reached / lost to follow-up.
7. The study investigator suspends or terminates the study.
8. Other unanticipated reason.

Any subject who prematurely discontinues the study should complete the week 24 (End of Study) assessments and subjects should be encouraged return 4 weeks later for the safety follow up visit.

6. ADVERSE EVENTS

ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, PREGNANCY, & PRODUCT QUALITY COMPLAINTS

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.

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

The protocol must include a definition for Serious Adverse Events (SAE)**.**

SERIOUS ADVERSE EVENTS

A **S*erious 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 (see **NOTE** below)
- 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.

Below is supplemental information that is included in BMS-Sponsored trials. It is the responsibility of the Sponsor-Investigator to determine if this information regarding hospitalization is considered SAEs or not and whether it should be included in the protocol.

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-

threatening event)

- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

NOTE: Although pregnancy and potential drug-induced liver injury (DILI), are not always serious by regulatory definition, these events must be reported within the SAEs timeline.

NOTE: 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).

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

Related: 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.

An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS. If the Sponsor-Investigator prefers to a study specific/Institutional form, it must be sent to the BMS ISR Trial Manager prior to study initiation for internal BMS review to ensure that at a minimum all of the data elements on the CIOMS form are present.

Please include the BMS Protocol number 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

NOTE: If a CIOMS I or Medwatch form is selected for reporting, the investigator causal assessment must be provided in the narrative section, otherwise the BMS form must be used.

NOTE: For studies with long-term follow-up period in which safety data are being reported, include the definition of end date of SAE collection.

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.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved study specifi/institutional SAE form.

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.

NOTE: The Sponsor-Investigator must provide a single centralized e-mail address (not an individual's e-mail address) to be used by BMS to send AE/SAE report related queries. The single centralized e-mail address must be provided in the Study Contract

and sent to aepbusinessprocess@bms.com.

Expedited and periodic safety update reporting by BMS:

It is the Sponsor-Investigator's responsibility to report events to their Local HA. In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

In accordance with local regulations, BMS will notify Sponsor-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)**. Sponsor-Investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report. Sponsor-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 Sponsor-Investigator or BMS decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the Sponsor-Investigator **must review and retain the ESR with the IB**. Where required by local regulations or when there is a central IRB/IEC for the study, the Sponsor-Investigator will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

NON-SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The collection of non-serious AE information should 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.

PREGNANCY

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).

The Sponsor-Investigator must immediately notify **Worldwide.Safety@bms.com** of this event and complete one of the following forms **within 24 hours of awareness** of the event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with **SAE reporting procedures.**

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the **CIOMS, MedWatch, BMS Pregnancy Surveillance Form, or approved site SAE form**. A BMS Pregnancy Surveillance Form may be provided upon request.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor-Investigator or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

LABORATORY TEST ABNORMALITIES

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

OTHER SAFETY CONSIDERATIONS

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-

serious or serious AE, as appropriate, and reported accordingly.

ADVERSE EVENT REPORTING FOR SPECIFIC SITUATIONS (remove if not applicable):

- **Assets with no marketing authorization: Potential Drug Induced Liver Injury (DILI)**

Definition of criteria is mandatory for **all pre-marketed asset protocols** enrolling participants without known abnormalities in liver function at baseline AND for protocols involving participants with known liver abnormalities at baseline or with other clinical confounders where asset specific criteria for potential drug induced liver injury have been defined. Use for marketed assets is optional.

For protocols without known abnormalities in liver function at baseline, use the mandatory standard DILI definition listed below. Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, **must be reported as SAEs.**

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

- **Immune-Mediated AEs (Product Specific, Usually a regulatory requirement)**

Immune-Mediated AEs are required in **ISR Protocols with Registrational Intent**.

Every AE must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information must be collected.

Immune-mediated adverse events (IMAEs) are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected.

- **AEs of Interest**

ADVERSE EVENT RECONCILIATION PROCESS

AEIs may be serious or non-serious and may require further investigation to better characterize and understand them. In the deucravacitinib clinical development program, select infections (opportunistic, TB, herpes zoster) and malignancies have been identified as AEIs based on the mechanism of action of deucravacitinib. Therefore, in order to better characterize and understand these AEIs, information may be collected on supplemental CRFs. Additionally, information on potential AEIs based on the disease or population under study may be collected on supplemental CRFs.

The Sponsor-Investigator (or designee) will reconcile the clinical database AE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).

- The Sponsor-Investigator will request the SAE reconciliation report (and include the BMS protocol number) from BMS GPV&E (aepbusinessprocess@bms.com) every 3 months and prior to data base lock or final data summary
- GPV&E will send the Sponsor-Investigator the report to verify and confirm all AE and SAEs have been transmitted to BMS GPV&E.
- The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Sponsor-Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS (Worldwide.Safety@bms.com).

PRODUCT QUALITY COMPLAINTS (PQCs)

Definition

Any communication about a **BMS Product** that alleges deficiencies related to identity, quality, durability, reliability, safety, effectiveness, performance, tampering, diversion, and/or counterfeiting/falsification of a drug, combination product, or device after it is released for distribution to market or clinic by either: (1) BMS or (2) distributors or partners for whom BMS manufactures the material. This includes all components co-packaged with the drug, such as drug containers, delivery system, labelling, and inserts.

BMS product: Commercial or investigational materials (i.e., drugs, devices, biologics or any combination thereof) and their packaging components, whether they are produced or distributed by BMS or by third parties under contract with BMS, and products that are being manufactured for BMS by third parties.

Reporting

Product Quality Complaints must be reported to BMS **within one (1) business day** of awareness to **IMPQualityComplaints@bms.com.**

In the event of a suspected product quality issue, the affected product must be quarantined immediately at the Investigational site.

The affected product should not be disposed unless retention presents a risk to personnel (e.g., cytotoxic, risk of injury from broken glass or sharps).

When reporting, as much product information as possible should be reported. At a minimum, but not limited to, include:
ISR Study number, site reference, product description, impacted batch number, container number(s), photographs, and any other supporting information.

7 INVESTIGATIONAL PRODUCT HANDLING

7.1 Investigational Product Receipt

At study initiation and as needed thereafter, deucravacitinib and Enstilar will be shipped to a responsible person at the investigator's institution, who will check the amount and condition of the drug, and maintain a record of this information.

7.2 Investigational Product Storage

Investigational product will be stored per the storage conditions identified on drug label. At the study site, all IP will be stored in a locked, safe area to prevent unauthorized access.
Records of the actual storage conditions during the period of the study will be maintained.

8 RECORD RETENTION

The investigator must retain these documents according to local laws or requirements. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC; Composition of the IRB/EC;
- Record of all communications between the Investigator and Bristol Myers Squibb.
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- All other source documents (subject records, hospital records, laboratory records, etc);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Bristol Myers Squibb if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Bristol Myers Squibb prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Bristol Myers Squibb for permission to make alternative arrangements. Details of these arrangements should be documented. All study documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

8.1 Study Monitoring

The investigator will self-monitor all study records for accuracy, completeness, and compliance with the protocol and GCPs and federal regulations. All study records will be made available to Bristol Myers Squibb representatives upon request. Study site facilities and study records will be made available to regulatory authorities' inspectors if an inspection takes place. The investigator will notify Bristol Myers Squibb if this occurs.

8.2 Statistical Considerations

It is desired to enroll 30 patients. Since this is a pilot study with no formal hypothesis testing, statistical power/sample size is not formally presented in this protocol.

The study will analyze data based on the non-responder imputation (NRI) method. This will be performed for each arm of the study (PASI 75 responders at week 8 and PASI 25-74 responders at week 8. Subjects who do not complete week 12 assessments will be classified as non-responders

Analysis will be performed by the Investigator on proportion of subjects achieving Psoriasis Area Severity Index (PASI) 75 response at week 12

The investigator will also analyze PASI 25-74 at week 8, PASI, PGA, BSA, PGAxBSA and DLQI improvement at week 8, BSA, PGA and BSA x PGA and DLQI improvement at week 12. PASI, BSA, PGA, BSA x PGA and DLQI at weeks 16, 20 and 24. This analysis will be done separately for both cohorts (PASI 75 responders at week 8 and PASI25-74 responders at week 8) using summary statistics. The Investigator will also analyze SAE's by cohort.

8.2.1 Exploratory Analysis

Additional exploratory analysis may be detailed in and performed according to a separate statistical plan at the discretion of sponsor-investigator.

8.3 Schedule of Events

Procedure	Screening	BASELINE	Week4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28 Safety FU
Informed Consent	X								
Demographics/Medical History	X	X							
Inclusion/Exclusion	X	X							
Physical Exam	X	X		X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test	X								
Urine Pregnancy Test		X	X	X	X	X	X	X	X
Serum Chemistry, Hematology & Fasting Lipids	X					X			**x**
Quantiferon Gold, HBV, HBC, HIV	X								
PASI	X	X		X	X	X	X	X	
BSA	X	X		X	X	X	X	X	
PGA	X	X		X	X	X	X	X	
DLQI		X		X	X	X	X	X	
Vital Signs	X	X		X	X	X	X	X	X
Photography		X		X	X	X	X	X	
Deucravacitinib dispensing		X	X	X	X	X	X		
Enstilar dispensing				X					
IP accountability			X	X	X	X	X	X	

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7. APPENDICES

Appendix A
Subject Diaries

Storage

●Keep study medication at room temperature.
●Keep out of reach of children

Enstilar Dosing

●Apply once daily
●Do not apply on face, underarms or groin
●Avoid heat, flames or smoking when applying.
●Do not bandage, cover, or wrap the treated area
●Apply to affected areas and gently rub in.
●Avoid bathing, showering or swimming right after applying the study medication.

Dosing Diary

●Record all doses on the diary as soon as possible.
●Return diary and medication to all of your appointments.
●Record any comments or information in "remarks" section for missed dose, adverse event, or change in medication.
●Please make recordings clear and legible.

	Date (MMM/DD)	Dose (Circle One)	Time (HH:MM)	Remark
Ex	Jan/01	AM / PM	0800	
1		AM / PM		
2		AM / PM		
3		AM / PM		
4		AM / PM		
5		AM / PM		
6		AM / PM		
7		AM / PM		
8		AM / PM		
9		AM / PM		
10		AM / PM		
11		AM / PM		
12		AM / PM		
13		AM / PM		
14		AM / PM		

	Date (MMM/DD)	Dose (Circle One)	Time (HH:MM)	Remark
15		AM / PM		
16		AM / PM		
17		AM / PM		
18		AM / PM		
19		AM / PM		
20		AM / PM		
21		AM / PM		
22		AM / PM		
23		AM / PM		
24		AM / PM		
25		AM / PM		
26		AM / PM		
27		AM / PM		
28		AM / PM		

Appendix B

Physician's Global Assessment

Physician's Global Assessment (PGA)

Score	Grade	Definition
0	**Clear**	Plaque elevation = 0 (no elevation) Scaling = 0 (no scale) Erythema = 0 (residual post-inflammatory hyperpigmentation or hypopigmentation may be present)
1	**Minimal**	Plaque elevation = ± (possible, but difficult to ascertain whether there is a slight elevation) Scaling = ± (surface dryness with some white coloration) Erythema = up to moderate (up to definite red color)
2	**Mild**	Plaque elevation = slight (slight, but definite elevation, typically edges are indistinct or sloped) Scaling = fine (fine scale partially or mostly covering lesions Erythema = up to moderate (up to definite red coloration)
3	**Moderate**	Plaque elevation = moderate (moderate elevation with rough or sloped edges) Scaling = coarser (course scale covering most of all of the lesions) Erythema = moderate (definite red coloration)
4	**Severe**	Plaque elevation = marked (marked elevation typically with hard or sharp edges) Scaling = course (course, non-tenacious scale predominates) Erythema = severe (very bright red coloration)
5	**Very Severe**	Plaque elevation = very marked (very marked elevation typically with hard sharp edges) Scaling = very coarse (course, thick tenacious scale of over most of all of the lesions; rough surface) Erythema = very severe (extreme red coloration; dusky to deep red coloration)

Appendix C

Psoriasis Area Index Severity

PASI Scoring

Four anatomic sites – head, upper extremities, trunk, and lower extremities – are assessed for erythema, induration (plaque thickness), and desquamation (scaling) as seen on the day of the examination. The severity of each sign is assessed using a 5-point scale:

- 0 = No symptoms
- 1 = Slight
- 2 = Moderate
- 3 = Marked
- 4 = Very marked

The table below outlines the characteristics of each category.

	Erythema[a]	Desquamation	Induration
0 = none	No redness	No scaling	No elevation over normal skin
1 = slight	Faint redness	Fine scale partially covering lesions	Slight but definite elevation, typically edges indistinct or sloped
2 = moderate	Red coloration	Fine to coarse scale covering most of all of the lesions	Moderate elevation with rough or sloped edges
3 = marked	Very or bright red coloration	Coarse, non-tenacious scale predominates covering most or all of the lesions	Marked elevation typically with hard or sharp edges
4 = very marked	Extreme red coloration; dusky to deep red coloration	Coarse, thick, tenacious scale over most or all lesions; rough surface	Very marked elevation typically with hard sharp edges

a. Do not include residual hyperpigmentation or hypopigmentation as erythema.

Appendix D

Dermatology Life Quality Index

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant ❒
	If "No", over the last week how much has your skin been a problem at	A lot A little	❒ ❒	

	work or **studying**?	Not at all	❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.