Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

Project Title:	Deucravacitinib for the Treatment of Palmoplantar Pustulosis
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2 PROTOCOL SUMMARY

Protocol Title:	Deucravacitinib for the Treatment of Palmoplantar Pustulosis
Background:	Palmoplantar pustulosis (PPP) is a chronic, orphan disease associated with significant morbidity. Previously considered a subtype of psoriasis, important differences identified in the immune dysregulation between psoriasis and PPP suggest they are distinct entities. Because of these important differences in the inflammatory profile, patients with PPP have an unpredictable and frequently inadequate response to therapies that are highly effective for plaque psoriasis. There are currently no FDA approved treatments specifically for PPP and few prospective trials have been performed specifically in these patients. Deucravacitinib is a novel, selective TYK2 inhibitor with a unique mechanism of action compared to other Janus kinase (JAK) inhibitors. Deucravacitinib binds to the regulatory pseudokinase domain of TYK2 rather than to the active adenosine triphosphate–binding site in the catalytic domain of TYK2. Binding by deucravacitinib allosterically locks the regulatory domain, inhibiting the interaction with the catalytic domain. This blocks activation of TYK2, inhibiting TYK-2 mediated signaling of by cytokines involved in the psoriasis pathogenesis including IL-23, IL-12 and Type 1 interferon. Deucravacitinib has previously demonstrated efficacy in Phase II/III trials of plaques psoriasis. Given that IL-12 and IL-23 are involved in the pathogenesis of both plaque psoriasis and palmoplantar pustulosis, deucravacitinib is an exciting potential novel therapy for this orphan disease.
Study Descriptions:	A prospective, single-arm, open-label trial of deucravacitinib 6 mg daily in patients with PPP. All participants will receive deucravacitinib 6 mg daily for 24 weeks, with study visits every 4 weeks.
Objectives:	1. Evaluate the efficacy of deucravacitinib in adults with PPP 2. Evaluate the impact of deucravacitinib on quality of life in adults with PPP 3. Evaluate the safety of deucravacitinib
Primary Endpoint:	• Proportion of participants who achieve a ppPASI-50 response, or at least 50% improvement in ppPASI score, at 16 weeks
Secondary Endpoints:	• Proportion of participants who achieve at least 50% improvement in the palmoplantar pustular psoriasis area and severity index (ppPASI-50) at 24 weeks • Frequency of participants with adverse events • Change from baseline in the Dermatology Quality of Life Index • Change from baseline in ppPASI • Percentage of patients who achieved a static Physician's Global Assessment score of 0/1 • Change from baseline in the EQ-5D VAS score • Change from baseline in itch VAS • Change from baseline in pain VAS
Inclusion Criteria:	• Adults aged 18 years of age and older • Dermatologist confirmed diagnosis of PPP for at least 6 months • Moderate-severe PPP, defined as a ppPASI $\geq$ 12 • Inadequate response to topical therapy and a candidate for systemic or phototherapy • Willing to discontinue current topical and/or systemic PPP treatments, except for OTC emollients • Willing to use acceptable contraception methods or maintain abstinence for the duration of the study
Exclusion Criteria:	• Participants with other immune-mediated conditions requiring concurrent systemic immunosuppressant treatments • Current/recent administration of PPP-specific medications including: o Rituximab within 6 months of the baseline visit

	○ Biologics within 12 weeks of baseline visit ○ Systemic steroids, oral immunosuppressants (azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus), oral retinoids (acitretin, isotretinoin), apremilast, or dapsone within 4 weeks of baseline visit ○ Phototherapy within 4 weeks of baseline visit ○ Prescription topical medications (including calcineurin inhibitors, crisaborole, retinoids, steroids, tar, vitamin D analogs) within 2 weeks of baseline visit • History of active infection and/or febrile illness within 7 days; or infection requiring antibiotic treatment within 30 days; or serious infection requiring hospitalization and/or IV antibiotics within 90 days • Evidence of other infection including: ○ Active or untreated latent tuberculosis, defined as radiographic or laboratory evidence of active TB or positive quantiferon or PPD, unless the subject has completed the recommended treatment ○ Human immunodeficiency virus infection (positive HIV antibody) ○ Active hepatitis B ○ Active hepatitis C • Evidence of clinically significant laboratory abnormality including: ○ Absolute WBC count < 3000/mm3 ○ Platelet count < 100,000/mm3 ○ Hemoglobin < 9.0 g/dl ○ ALT or AST > 3 times the upper limit of normal • History of cancer within the past 5 years, excluding treated non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma) • Other uncontrolled chronic medical condition that may interfere with a patient's ability to participate in the clinical trial • Major surgery within 4 weeks of baseline visit • Receipt of live vaccine within 8 weeks of baseline visit • Pregnant or breastfeeding individuals • Inability to comply with any of the study procedures • Individuals who are incarcerated or compulsory detained
Sample Size:	A modified Simon's two-stage design will be used to maximize the safety and efficiency of this clinical trial in an orphan disease. In the first stage, 8 patients will be accrued. If 2 or fewer patients achieve a ppPASI-50 in these 8 patients, the study will be stopped. Otherwise, 10 additional patients will be accrued for a total of 18.
Analysis Plan:	Descriptive statistics will be used to characterize the study population, including demographics, disease characteristics and previous treatments. For the primary outcome, the percentage of participants who achieve a ppPASI-50 response, or at least 50% improvement in ppPASI score, at 16 weeks, the response rate with a 95% CI will be calculated. For all secondary endpoints, summary and descriptive statistics will be used as appropriate , including number of observations, calculation of mean/median, standard deviation range and 95% confidence intervals.

3 BACKGROUND AND SIGNIFICANCE

Palmoplantar pustulosis (PPP) is a limited form of pustular psoriasis characterized by persistent, sterile macroscopic pustules on the palms and/or soles[1] and associated with significant morbidity. PPP is a rare disease with an estimated one-year prevalence between 0.005% - 0.12%.[1-3] It has been reported as a solitary disease and in patients with a history of plaque psoriasis.

Previously considered a subtype of psoriasis, important differences identified in the immune dysregulation between psoriasis and PPP suggest they are distinct entities. Genetic susceptibility to plaque psoriasis is polygenetic, with 63 genes accounting for 28% of the heritibility.[4] Genes associated with antigen presentation, keratinocyte proliferation and differentiation, and production of pro-inflammatory cytokines in TH-17 cells all play an important role.[5] A different genetic profile has been associated with pustular psoriasis. Coding mutations in IL36RN, CARD14, AP1S3, SERPINA3, and MPO that affect IL-1 and IL-36 signaling have been associated with the clinical spectrum of pustular psoriasis.[5] Additionally, the inflammatory profiles between plaque psoriasis and pustular psoriasis have key differences. Plaque psoriasis is a T-cell mediated disease, largely driven by the IL-23/Th-17 pathway.[6] Overexpression of IL-23 by activated dendritic cells stimulates Th-17 differentiation, cell survival, and proliferation, resulting in the production of additional cytokines: IL-17A, IL-22, and INF-c. These cytokines cause the activation and hyperproliferation of keratinocytes, resulting in the characteristic plaque development.[7] In PPP IL-8, IL-36 gamma and IL-36Ra have been found to be overexpressed in lesional skin.[8] The IL-17A pathway is thought to play a more important role in PPP compared to plaque psoriasis.[9]

Because of these important difference in the inflammatory profile, patients with PPP have an unpredictable and frequently inadequate response to therapies that are highly effective for plaque psoriasis. There are currently no FDA approved treatments for PPP, and therefore, in the current standard practice, much of the information regarding treatment is adapted from plaque psoriasis. A Cochrane Review published in 2020 concluded that evidence is lacking for the efficacy of all chronic PPP treatments.[10] The few randomized control trials that have been performed are small and sometimes also include palmar plantar psoriasis, which complicated interpretation of the results. We recently published a retrospective cohort of 197 PPP patients from across the United States where more than 20 different treatments were tried in patients with PPP and a median of 6 visits per year of follow-up, suggesting a lack of effective treatments to control this chronic disease.[11]

Case reports suggest that off-label use of Janus kinase (JAK) inhibitors may be effective in the treatment of PPP. The JAK kinase family consists of 4 intracellular tyrosine kinases: JAK1, JAK2, JAK3 and TYK2.[12] JAK activation occurs via binding of a cytokine to JAK associated type I and II receptors. Activated JAKs initiate transphosphorylation, initiating the recruitment of signal transducers and activators of transcription (STAT) proteins. The JAK-STAT pathway mediates signaling downstream of receptors for Type I and Type II cytokines, including IL-6, IL-10, IL-12, IL-22, IL-23, interferon (IFN)-α, IFN-β, and IFN-γ, important cytokines in a variety of chronic inflammatory diseases.[13] There are reports of successful treatment of PPP, with both tofacitinib, an oral JAK1 and JAK3 inhibitor[14-17] and also baricitinib, an oral JAK1 and JAK2 inhibitor.[18]

Deucravacitinib is a novel, selective TYK2 inhibitor with a unique mechanism of action from other Janus kinase (JAK) inhibitors. Deucravacitinib binds to the regulatory pseudokinase domain of TYK2 rather than to the active adenosine triphosphate–binding site in the catalytic domain of TYK2, where other JAK

inhibitors bind. Binding by deucravacitinib allosterically locks the regulatory domain, inhibiting the interaction with the catalytic domain. This blocks activation of TYK2, inhibiting TYK-2 mediated signaling of by cytokines involved in the psoriasis pathogenesis including IL-23, IL-12 and Type 1 interferon.[19]

Deucravacitinib has previously demonstrated efficacy in phase II and phase III trials of plaque psoriasis. In the Phase 2 randomized, double-blind, parallel-group, clinical study of increasing doses deucravacitinib placebo in subjects with moderate to severe PsO. The Deucravacitinib treatment demonstrated a dose-dependent improvement in PASI 75, with the 3 highest doses of 3 mg BID, 6 mg BID, and 12 mg QD showing similar responses of 68.9%, 66.7%, and 75.0%, respectively, versus placebo response of 6.7%.[20] In the 2 Phase III studies in psoriasis (NCT03624127, NCT03611751), deucravacitinib demonstrated robust and statistically significant efficacy compared with placebo and apremilast, with clinically meaningful improvements in multiple clinical and quality of life parameters in a broad population of patients with moderate-to-severe psoriasis naive to prior treatment or treatment experienced.[21] Given that IL-12 and IL-23 are involved in the pathogenesis of both plaque psoriasis and palmoplantar pustulosis, deucravacitinib is an exciting potential novel therapy for an orphan disease and further investigation is warranted.

4 OBJECTIVES & ENDPOINTS

4.1 Objectives

- Evaluate the efficacy of deucravacitinib in adults with PPP
- Evaluate the impact of deucravacitinib on quality of life in adults with PPP
- Evaluate the safety of deucravacitinib

4.2 Primary Endpoint

- Proportion of participants who achieve at least 50% improvement in the palmoplantar pustular psoriasis area and severity index (ppPASI-50) at 16 weeks.
- **Hypothesis:** 50% of patients treated with deucravacitinib 6 mg once daily for 16 weeks will achieve at least 50% improvement in disease severity (ppPASI-50)

4.3 Secondary Endpoints

- Frequency of patients with adverse events at week 16 & 24
- Change from baseline in the Dermatology Quality of Life Index (DLQI) at week 16 & 24
- Change from baseline in ppPASI at week 16 & 24
- Percentage of patients who achieved a Physician's Global Assessment score of 0 or 1 at week 16 & 24
- Change from baseline in the EQ-5D VAS score at week 16 & 24
- Change from baseline in itch VAS at week 16 and 24 weeks
- Change from baseline in pain VAS at week 16 and 24 weeks
- Proportion of participants who achieve at least 50% improvement in the palmoplantar pustular psoriasis area and severity index (ppPASI-50) at 24 weeks

5 GENERAL DESCRIPTION OF STUDY DESIGN

This is a prospective, single-arm, open-label trial of deucravacitinib 6mg once daily in patients with PPP. All participants will receive deucravacitinib 6 mg once daily for 24 weeks, with study visits every 4 weeks. The study schema can be found in Appendix A.

6 SUBJECT SELECTION & ELIGIBILITY

6.1 Recruitment Strategies

Male and female participants representing all ethnic groups and racial categories will be recruited for this study. Recruitment strategies may include:

- Referrals from study site-specific physicians and physicians in the surrounding communities
- Targeted Research Announcements
- Institutional and lab-specific clinical research websites
- Advertisements on the internet, including clinicaltrials.gov and in-print media advertisements
- Interactions with patient and physician organizations in the local and national dermatology community

6.2 Inclusion Criteria

- Adults aged 18 years of age and older
- Dermatologist confirmed diagnosis of PPP for at least 6 months
- Moderate-severe PPP, defined as a ppPASI $\geq$ 12
- Inadequate response to topical therapy and a candidate for systemic or phototherapy
- Willing to discontinue current topical and/or systemic PPP treatments, except for OTC emollients
- Willing to use acceptable contraception methods or maintain abstinence for the duration of the study

6.3 Exclusion Criteria

- Participants with other immune-mediated conditions requiring concurrent systemic immunosuppressant treatments
- Current/recent administration of PPP-specific medications including:
  - Rituximab within 6 months of the baseline visit
  - Biologics (including adalimumab, anakinra, brodalumab, certrolizumab, etanercept, golimumab, guselkumab, infliximab, ixekizumab, rizankizumab, secukinumab, spesolimab, tildrakizumab, ustekinumab) within 12 weeks of baseline visit.
  - Systemic steroids, oral immunosuppressants (azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus), oral retinoids (acitretin, isotretinoin), apremilast, or dapsone within 4 weeks of baseline visit
  - Phototherapy within 4 weeks of baseline visit
  - Prescription topical medications (including calcineurin inhibitors, crisaborole, retinoids, steroids, tar, vitamin D analogs) within 2 weeks of baseline visit

- History of active infection and/or febrile illness within 7 days; or infection requiring antibiotic treatment within 30 days; or serious infection requiring hospitalization and/or IV antibiotics within 90 days
- Evidence of other infection including:
    - Active or untreated latent tuberculosis, defined as radiographic or laboratory evidence of active TB or positive quantiferon or PPD, unless the subject has completed the recommended treatment)
    - human immunodeficiency virus infection (positive HIV antibody)
    - Active hepatitis B
    - Active Hepatitis C
- Evidence of clinically significant laboratory abnormality including:
    - Absolute WBC count < 3000/mm3
    - Platelet count < 100,000/mm3
    - Hemoglobin < 9.0 g/dl
    - ALT or AST > 3 times the upper limit of normal
- History of cancer within the past 5 years, excluding treated non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma)
- Other uncontrolled chronic medical condition that may interfere with a patient's ability to participate in the clinical trial
- Major surgery within 4 weeks of baseline visit
- Receipt of live vaccine within 8 weeks of baseline visit
- Pregnant or breastfeeding individuals
- Inability to comply with any of the study procedures
- Individuals who are incarcerated or compulsory detained

7 SUBJECT ENROLLMENT & INFORMED CONSENT

7.1 Enrollment

- Subjects will be pre-screen by study staff over the telephone.
- Those who meet the telephone screening criteria will be brought to clinic for a screening visit.
- Before any study procedures are performed, subjects will have the details of the study described to them, and they will be given a written informed consent document to read. Then, if subjects consent to participate in the study, they will indicate their consent by signing and dating the informed consent document in the presence of study personnel.
- After consent has been obtained, the participant will participate in a screening visit to determine eligibility including review of inclusion/exclusion criteria, physical exam with disease severity measures and laboratory evaluation as detailed in Appendix B.
- Patients will be notified of eligibility by phone when all results are available and baseline visit will be scheduled.

7.2 Informed Consent

- We will use the REDCap eConsent feature to collect digital signatures, during the in person Informed Consent Process the investigators will:
    - Provide a paper copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation.

The language must be non-technical and easily understood. Interpreters will be available (in person or telephone) for all participation whose preferred language is not English.
    - Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
    - Obtain an electronic signature of the informed consentand dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. Once all e-signatures are collected, the patient will receive a copy of the fully signed consent via email.
- If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.
- The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

7.3 Ethical Considerations

- This study will be conducted under the ethical principles that have their origin in the Declaration of Helsinki and in accordance with Good Clinical Practice In accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH), WHO and any local directives.
- The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study, with personnel who are qualified by education, training, and experience to perform their respective tasks and that the study will not use the services of study personnel for whom sanctions have been invoked or where there has been scientific misconduct or fraud

8 STUDY ASSESSMENTS & PROCEDURES

8.1 Study Drug

- **Investigational Product (IP):** All study participants will receive deucravacitinib 6mg once daily for a maximum of 24 weeks while enrolled in the study.
- **Storage**: The IP will be stored in a secure area in accordance with the package insert. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and BMS should be contacted immediately. A current disposition record of study drug (supplied by BMS) will to be maintained at each study site where study drug is inventoried and dispensed.
- **Blinding/Unblinding**: N/A
- **Medication Compliance**: At each study visit compliance with study drug will be reinforced. Diaries will be used to assist subjects in maintaining an accurate assessment of daily pill intake. Subject diaries and returned pill bottles will be required to be returned at every visit.

- **Disposal:** Disposal of unused medication will occur according to applicable regulations, guidelines, and institutional procedures.

8.2 Study Events

At the initial screening visit, after informed consent is obtained, eligibility will be determined through review of inclusion/exclusion criteria and physical exam with determination of disease severity measures. If the patient is deemed eligible to participate, demographic and medical history information will be collected and laboratory evaluation, including CBC, CMP, CPK, triglycerides, HIV test, Quantiferon TB-Gold, Hep B surface antigen, Hep C antibody and urine pregnancy test (as applicable) will be performed. Any labs (except urine pregnancy test) checked in the 90 days prior to the screening visit, as a part of routine clinical care, can be used as a part of the screening labs.

All patients who meet all study eligibility criteria will be scheduled for a baseline study visit within 2 weeks of the screening visit. All study participants will receive deucravacitinib 6 mg once daily for 24 weeks or until participation from the trial is discontinued. Participants will be evaluated with clinical instruments (ppPASI, PGA, DLQI, EQ5D-5L, VAS-itch, VAS-pain) and clinical photographs every 4 weeks for the duration of the study. Additionally, safety assessment of new symptoms/side effects will be asked at every visit and safety labs will be performed at week 16 and week 24. **Please see the Time and Events Schedule (Appendix B) for full details.**

8.3 Study Assessments

The following clinical assessments will be used in the study:

- **Palmoplantar Pustulosis Psoriasis Area and Severity Index (ppPASI) (Appendix C):** The ppPASI is the most commonly used disease severity measure use in palmoplantar pustulosis clinic trials. The ppPASI is composed of subscores of erythema (E), pustules/vesicles (P), desquamation/scales (D) on the left (L) and right (R) palm (P) and sole (S) respectively. The PASI produces a numeric score that can range from 0 to 72, with higher PASI scores denoting more severe disease activity. The ppPASI is calculated using following formula:

  PPPASI=(E+P+D) Area*0.2 (RP)+(E+P+D) Area*0.2 (LP)+ (E+P+D) Area*0.3 (RS)+(E+P+D) Area*0.3 (LS).

- **Physician Global Assessment (PGA) (Appendix D):** The physician's global assessment is a widely used outcome measure that relies on physician visual assessment of disease severity. The static PGA determines psoriasis severity at a single point in time, without taking the baseline disease condition into clear (0), almost clear (1), mild (2), moderate (3), severe (4).

- **Dermatology Life Quality Index (DLQI) (Appendix E):** The DLQI is a dermatology-specific quality of life instrument to measure the impact of skin disease on different aspects of health-related quality of life. The questionnaire contains 10 questions, each scored on a 4-point Likert scale.[22] The DLQI is calculated by adding the score of each question, resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. A score higher than 10 indicates that the patient's life is being severely affected by

their skin disease. The minimal clinically important difference in inflammatory skin disease is a change of 4 points.[23] The DLQI is the most frequently used patient reported outcome measure in randomized controlled trials in dermatology.

- **EuroQol-5D (EQ-5D-5L) (Appendix F):** The EQ-5D is a validated, reliable, and responsive instrument widely used in clinical trials where respondents rate their health in each of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety depression.[24] This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. EQ-5D questionnaire also includes a Visual Analog Scale (VAS), by which respondents can report their perceived health status with a grade ranging from 0 (the worst possible health status) to 100 (the best possible health status).

- **Visual Analog Scale, Itch (Appendix G):** The itch visual analogue scale (VAS-itch) is a patient reported pruritis assessment that has been shown to be valid and reliable in the measurement of pruritis and is widely used in dermatology clinical trials.[25,26] The VAS-itch is a 10 cm line on which patients mark their pruritus intensity on a scale from "no itch" (0 points) to "worst imaginable itch" (10 points).[27] The VAS-itch can be interpreted as 0–< 3 points represents mild pruritus, ≥ 3–7 points moderate pruritus, ≥ 7–9 points severe pruritus, and ≥ 9 points severe pruritus.[28]
- **Visual Analog Scale, Pain (Appendix H):** The pain visual analogue (VAS-pain) is a patient reported instrument that measures pain intensity. Patients are asked to place a line perpendicular to the VAS line at the point that represents their pain intensity over the past 24 hours. It has been widely used in diverse adult populations, including those with rheumatic diseases.[29] The VAS-pain is a continuous 10cm line, anchored by 2 verbal descriptors, one for each symptom extreme. The following cut points on the pain VAS have been recommended to measure postsurgical pain: no pain (0–4 mm), mild pain (5–44 mm), moderate pain (45–74 mm), and severe pain (75– 100 mm.[30] In patients with rheumatoid arthritis, the minimal clinically significant change has been estimated as 1.1 points on an 11-point scale (or 11 points on a 100-point scale).[31]

- **(Optional) Photographs:** Standard medical dermatology photographs of the palms and soles will be taken as documented in Appendix B. A training session prior to study initiation to demonstrate proper photographic technique. Detailed instructions on the collection and transmission of digital images will be provided to the Investigator at the time of study initiation.

8.4 Safety Assessments

A complete physical examination, including measuring vital signs and complete blood count, complete metabolic panel, creatine phosphokinase and triglycerides will be performed at baseline, week 16 and EOS. Additionally, patients will be questioned regarding new symptoms at every visit. All safety lab tests will require the subject to be fasting for 8 hours prior to blood collection.

8.5 Subject Withdrawal

Subjects must discontinue deucravacitinib for any of the following reasons:

- Withdrawal of informed consent (a subject's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Noncompliance
- Pregnancy

All subjects who discontinue their participation in the study should comply with protocol-specified early termination procedures as outlined above. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely. If a subject withdraws before completing the study, the reason for withdrawal will be documented appropriately.

8.6 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, texts, or emails as well as lack of response by subject to one registered mail letter.

8.7 Renumeration

All participants will receive $90 for each completed study visit.

9 RISKS AND DISCOMFORTS

9.1 Known Drug Side Effects and Toxicities

The understanding of the safety of deucravacitinib is predominantly based on unblinded data from Phase 1 studies, Phase 2 studies in psoriasis and PsA, and Phase 3 studies in psoriasis. In the Phase 1 studies in healthy subjects, DEUC was safe in single doses from 1 to 40 mg and in multiple doses up to 24 mg/day (12 mg BID) for 14 days. Across the studies, the most common event related to deucravacitinib was acneiform rash, which appeared to be dose-related, with the highest incidence at the 12 mg BID dose. These reactions were all mild or moderate, non-serious, managed with topical treatment (when required), reversible, and rarely led to discontinuation of study drug.

In the Phase II clinical trial for patients with psoriasis, there were no significant changes from baseline in mean values of blood counts; serum levels of liver enzymes, lipids, creatinine, or immunoglobulins (IgM, IgA, IgG, and IgE); vital signs; or ECG findings. Cases of asymptomatic increases from baseline in creatine kinase levels were observed in 12 of 44 patients (27%) who received placebo and 57 of 221 (26%) who received deucravacitinib, with no dose dependence and no events resulting in discontinuation of the trial regimen. In participants in the Phase 2 trial who received 12mg daily (n = 44), the dose planned for this protocol, adverse events were reported in 77% of the patients as compared to 51% in the placebo group. Nasopharyngitis (5%), headache (5%), diarrhea (9%), nausea (5%), and upper respiratory tract infection (2%) were the most common adverse events in those treated with deucravacitinib 12mg daily.

The majority of deucravacitinib clinical data is from an integrated analysis of the completed pivotal Phase III studies (NCT03624127, NCT03611751) and the ongoing long-term extension study (NCT04036435) in psoriasis, which included 1,519 subjects exposed to deucravacitinib. Most of the AEs were mild or moderate in severity and the incidence of SAEs was low. In the 16-week placebo-controlled period the Phase III trials, the incidence of severe AEs and SAEs in the deucravacitinib group was generally similar to the placebo and apremilast groups, and the frequency of AEs leading to treatment discontinuation in the deucravacitinib group was 2.4%, compared to 3.8% for placebo and 5.2% for apremilast.

The proportions of subjects experiencing AEs in the class of "Infections and infestations" and "Skin and subcutaneous tissue disorders" were higher in the deucravacitinib group compared with the placebo and apremilast groups. The most common AEs reported in the deucravacitinib group in the placebo-controlled period were nasopharyngitis (9.0%), upper respiratory tract infection (5.5%), headache (4.5%), diarrhea (4.4%), blood CPK increased (2.7%), and arthralgia (2.3%). Among these AEs, events with a ≥ 1% higher incidence in the deucravacitinib group than placebo were upper respiratory tract infection (5.5% vs 4.1%) and blood CPK increased (2.7% vs 1.2%); none of these AEs was serious.

The reproductive risk potential has not been comprehensively evaluated in humans. DEUC should not be used in pregnant women.

9.2 Other Risks Associated with Study Procedures

Venipuncture: Risks of venipuncture include bruising, pain at site of phlebotomy, fainting, and rarely infection.

9.3 Privacy/Confidentiality Risks

Personal information may be contained in the copies of medical record. This information will be kept confidential by the investigators, and participants will not be identified by name in any publication.

10 BENEFITS

10.1 Known Potential Benefits to Participants

There are currently no FDA approved treatments for PPP and information regarding the efficacy of existing dermatology therapies is limited. JAK-STAT signaling is plays an important role in the activation of many cytokines involved in chronic inflammatory disorders, and therefore, inhibition of this JAK/STAT is an important therapeutic target. Case reports suggest that off-label use of Janus kinase (JAK) inhibitors may be effective in the treatment of PPP. There are reports of successful treatment of PPP, including TNF-induced PPP, with both tofacitinib, an oral JAK1 and JAK3 inhibitor[14-17] and also baricitinib, an oral JAK1 and JAK2 inhibitor.[18]

Deucravacitinib is a small molecule that blocks receptor-mediated TYK2, another member of the member of the JAK family.[32,33] TYK2 regulates the downstream signaling of interleukin (IL)-12, IL-23, and Type I interferon.[13] Deucravacitinib has previously demonstrated efficacy in phase II and phase III trials of plaque psoriasis. Given that IL-12 and IL-23 are involved in the pathogenesis of both plaque psoriasis

and palmoplantar pustulosis, deucravacitinib is an exciting potential novel therapy for an orphan disease and further investigation is warranted.

10.2 Known Potential Benefits to Society

Some research participants find participating in clinical trials to be a valuable experience, as their participation contributes to an increased understand about potential treatments for a rare disease like PPP.

11 Statistical Analysis

11.1 Data Collection

Protocol-specific case report forms will be developed and completed by the investigators during study visits and then entered into a study-specific RedCap database. REDCap (Research Electronic Data Capture) is a web-based application hosted by Mass General Brigham (MGB) Research Information Science & Computing (RISC), a HIPPA-compliant software application for electronic collection and management of research and clinical study data. Personal identifiers will not be used when collecting and storing data. An enrollment log will be maintained in the regulatory binder/file which is the only location of personal identifiers with unique subject identification number.

11.2 Sample Size

A modified Simon's two-stage design will be used to maximize the safety and efficiency of this clinical trial in an orphan disease.[34,35] Sample size was calculated based on the primary efficacy endpoint. The null hypothesis that the true rate of ppPASI is 20% will be tested against a one-sided alternative. In the first stage, 8 patients will be accrued. If 2 or fewer patients achieve a ppPASI-50 in these 8 patients, the study will be stopped. Otherwise, 10 additional patients will be accrued for a total of 18. The null hypothesis will be rejected if 7 or more patient achieve a ppPASI-50 in 18 patients. This design yields a type I error rate of 0.05 and power of 0.8 when the true response rate is 50%.

11.3 Data Analysis

Descriptive statistics will be used to characterize the study population, including demographics, disease characteristics and previous treatments. For the primary outcome, the percentage of participants who achieve a ppPASI-50 response, or at least 50% improvement in ppPASI score, at 16 weeks, the response rate with a 95% CI will be calculated. For all secondary endpoints, summary and descriptive statistics will be used as appropriate, including number of observations, calculation of mean/median, standard deviation range and 95% confidence intervals. The detailed methods are described in the statistical analysis plan.

12 Safety, Monitoring and Quality Assurance

12.1 Adverse Event Collection and Reporting Information:

- Adverse Event (AE): 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

- Non-serious adverse event: an AE not classified as serious
- Serious Adverse Event (SAE): 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)
  - [redacted]
  - results in persistent or significant disability/incapacity
  - is a congenital anomaly/birth defect
  - [redacted] or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
  - [redacted]
  - [redacted] (unless considered an important medical or life-threatening event)
- 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 (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.

12.2 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**.**
- 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 specific/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
- 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.

12.3 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.

12.4 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 400 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.

12.5 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.
- 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.

12.6 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 (e.g., anemia versus low hemoglobin value).

12.7 Other Safety Considerations:

- Any significant worsening noted during interim or final physical examinations, 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.

12.8 Adverse Event Reconciliation Process

- 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).

12.9 Product Quality Complaints (PQCs)

- Definitions:
  - 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

12.10 Data Safety Monitoring Plan

All data will be collected in a timely manner and reviewed by the principal investigator or co-investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations and violations will be immediately reported to the IRB, and if applicable to the Sponsor.

13 PRIVACY AND CONFIDENTIALITY

☒ Study procedures will be conducted in a private setting
☒ Only data and/or specimens necessary for the conduct of the study will be collected

- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☐ Additional privacy and/or confidentiality protections:
  N/A

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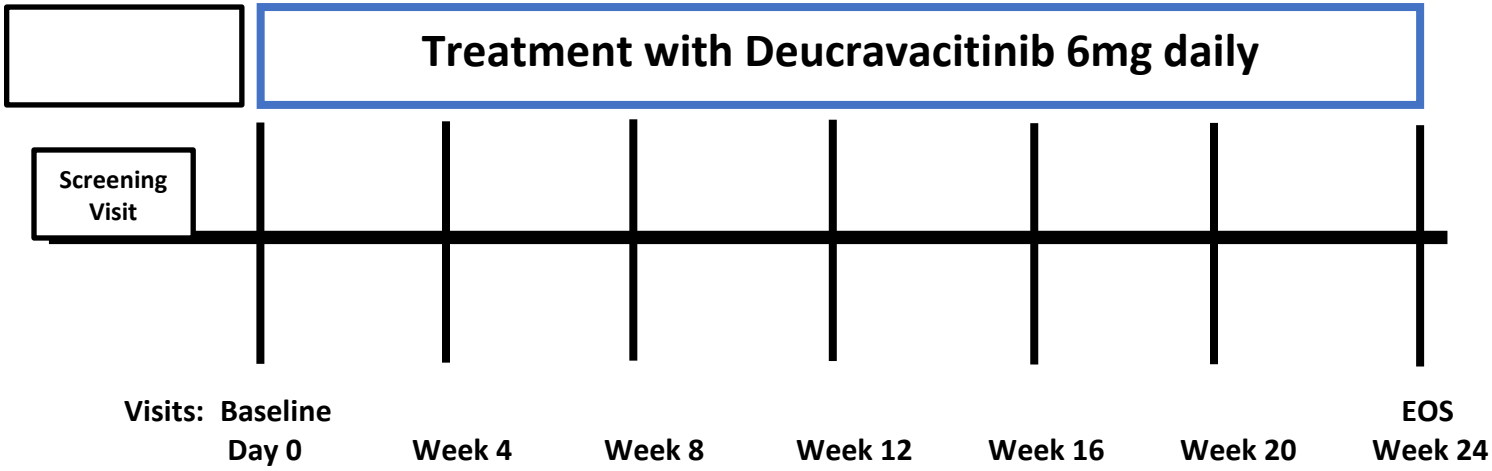
15 APPENDICES

15.1 Appendix A – Study Scheme



15.2 Appendix B – Study Assessments & Procedures

Visit	1 Screening	2 Baseline	3 Week 4	4 Week 8	5 Week 12	6 Week 16	7 Week 20	8 (EOS) Week 24	Early Termination
Informed consent	X								
Inclusion/exclusion criteria	X								
Medical history	X								
Prior/concurrent medications	X	X	X	X	X	X	X	X	X
New symptoms/side effects		X	X	X	X	X	X	X	X
Dispense study medication		X	X	X	X	X	X		
Assess medication compliance			X	X	X	X	X	X	X
Assessments									
Vital signs		X				X		X	X
Physical exam		X				X		X	X
ppPASI		X	X	X	X	X	X	X	X
PGA		X	X	X	X	X	X	X	X
DLQI		X	X	X	X	X	X	X	X
EQ-5D-5L		X	X	X	X	X	X	X	X
VAS-itch		X	X	X	X	X	X	X	X
VAS-pain		X	X	X	X	X	X	X	X
Photographs (Optional)		X	X	X	X	X	X	X	X
Laboratory Studies									
Urine pregnancy test	X								
CBC, CMP	X					X		X	X
HIV Test	X								
CPK	X					X		X	X
Triglycerides	X					X		X	X
Hep C antibody	X								
Hep B surface antigen	X								
QuantiFERON GOLD TB screen	X								

15.3 Appendix C – Palmoplantar Pustulosis – Psoriasis Area and Severity Index (ppPASI)

Disease severity (erythema (E), pustules/vesicles (P), desquamation/scales (D) and area involved) is assessed separately on the right palm, left palm, right sole and left sole.

Score	Erythema (E)	Pustules (P)	Desquamation (D)	Area Involved (%)
0	None	None	None	0
1	Slight	Slight	Slight	0 – 10
2	Moderate	Moderate	Moderate	11 – 30
3	Severe	Severe	Severe	31 – 50
4	Very Severe	Very Severe	Very Severe	51 – 70
5				70 – 90
6				91 - 100

Calculation of the Palmoplantar Pustulosis – Psoriasis Area and Severity Index (ppPASI):

ppPASI Score = [(right palm: E+P+D)*right palm_area*0.2] + [(left palm: E+P+D)*left palm_area*0.2] + [(right sole: E+P+D)*right sole_area*0.3] + [(left sole: E + P + D) *left sole_area * 0.3]

15.4 Appendix D – Physician's Global Assessment

Please score the patient's skin as a global assessment (palms and soles) on the disease present on your examination today.

	Score	Category	Description
	0	Clear	No visible signs of palmoplantar psoriasis
	1	Almost Clear	Just perceptible erythema, scaling and/or rare pustules
	2	Mild	Light pink erythema with few pustules
	3	Moderate	Pustules on a red erythematous base with or without, thickening of the skin
	4	Severe	Pustules, coalescing into lakes, dark red to violaceous plaques with scaling and thickening of the skin

15.5 Appendix E – Dermatology Life Quality Index

Patient ID: **Date:**

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check 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 **yard?**	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 **work** or **studying**?	A lot A little 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.

15.6 Appendix F – EuroQol-5D-5L

Please check the box that describes your health TODAY.

Mobility

- ☐ I have no problems walking
- ☐ I have slight problems walking
- ☐ I have moderate problems walking
- ☐ I have severe problems walking
- ☐ I am unable walk
- ☐

Self-Care

- ☐ I have no problems washing or dressing myself
- ☐ I have slight problems washing or dressing myself
- ☐ I have moderate problems washing or dressing myself
- ☐ I have severe problems washing or dressing myself
- ☐ I am unable to wash or dress myself

Usual Activities

- ☐ I have no problems doing my usual activities
- ☐ I have slight problems doing my usual activities
- ☐ I have moderate problems doing my usual activities
- ☐ I have severe problems doing my usual activities
- ☐ I am unable to do my usual activities

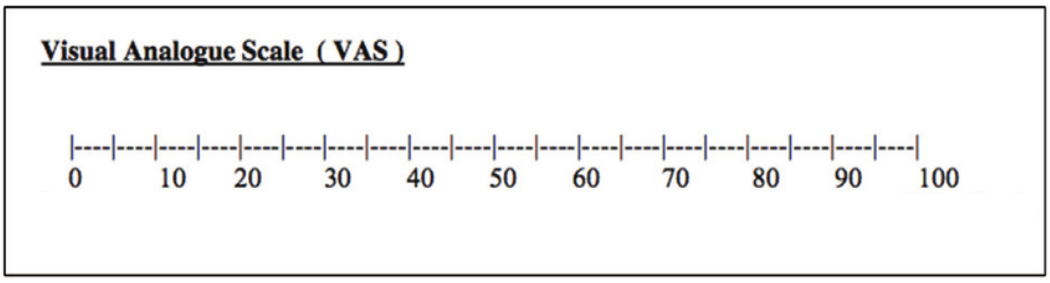
Pain/Discomfort

- ☐ I have no pain or discomfort
- ☐ I have slight pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have severe pain or discomfort
- ☐ I am in extreme pain or discomfort

Anxiety/Depression

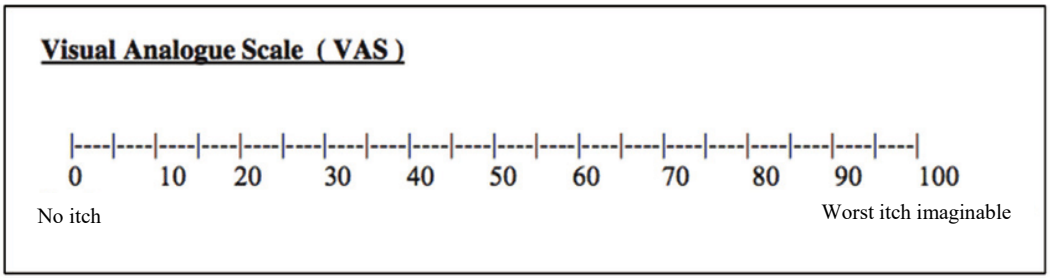
- ☐ I am not anxious or depressed
- ☐ I am slightly anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am severely anxious or depressed
- ☐ I am extremely anxious or depressed

We would like to know how good or bad your health is TODAY. This scale is numbered from 0 to 100. 100 means the best health you can imagine. 0 means the worse health you can imagine. Please click on the scale to indicate how your health is TODAY.



15.7 Appendix G – Visual Analog Scale, Itch

Please rate your itch over the past 24 hours.



15.8 Appendix H – Visual Analog Scale, Pain

Please rate your pain over the past 24 hours.