INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

**Clinical electronic Structured Harmonised Protocol**

**(CeSHarP)**

**M11 Template DEUCRALIP Example**

**“Investigator Initiated”**

|  |  |
| --- | --- |
|  | |
| **Full Title:** | Proof of concept study (multicenter, phase II) on the efficacy of the selective TYK2 inhibitor Deucravacitinib in Lichen planus patients (DEUCRALIP) |
| **Trial Acronym:** | DEUCRALIP |
| **Sponsor Protocol Identifier:** | DER-202201 |
| **Original Protocol:** | No |
| **Version Number:** | 3 |
| **Version Date:** | 07-NOV-2023 |
| **Amendment Identifier:** | 3 |
| **Amendment Scope:** | Global |
| **Compound Code(s):** | L04AA56 |
| **Compound Name(s):** | Deucravacitinib  SOTYKTU |
| **Trial Phase:** | Phase II |
| **Short Title:** | DEUCRALIP |
| **Sponsor Name and Address:** | Rheinische Friedrich-Wilhelms-Universität Bonn  represented by the Faculty of Medicine of the University of Bonn represented by the Dean of the Faculty of Medicine Venusberg-Campus 1, D-53127 Bonn  Prof. Dr. med. Joerg Wenzel Department of Dermatology and Allergology University Hospital of Bonn Venusberg- Campus 1, D-53127 Bonn |
| **Regulatory Agency Identifier Number(s):** | EU CT 2022-502991-21-00 |
| **Sponsor Approval Date:** | 07-NOV-2023 |

Sponsor Signatory:

Prof. Dr Joerg Wenzel on file or INSERT IMAGE HERE

**Medical Expert Contact:**

Prof. Dr. med. Joerg Wenzel Department of Dermatology and Allergology University Hospital of Bonn Venusberg- Campus 1, D-53127 Bonn

**SAE Reporting Method:** Report Serious Adverse Events to the sponsor. Refer to Section 9.4 for detailed reporting instructions.

Amendment Details

This protocol has been amended previously. Details of prior amendments are presented in Prior Protocol Amendment(s).

Current Amendment

The table below describes the current amendment.

|  |  |  |  |
| --- | --- | --- | --- |
| **Approximate #/% Enrolled at time of Sponsor Approval:** | Approximate ??% enrolled. | | |
| **Reason(s) for Amendment:** | Primary: See Amendment Summary | | Secondary: See Amendment Summary |
| **Amendment Summary:** | * Synopsis (Exclusion criteria) and chapter 9.3: Precision of exclusion criterion 3, adaption of exclusion criterion 12, addition of exclusion criteria 13 and 14, renumbering of the following exclusion criteria, precision of exclusion criteria 17 to 20 * Synopsis (Statistical Rationale) and chapter 14.2.3: Addition of description of primary endpoint for sample size rationale * Chapters 2.1, 2.3.1, 9.5.1, 9.5.2, 11.2 and 11.2.1: Deletion of prescreening visit * Chapter 9.3, 9.5.3 and 18.8: Deletion of all text passages about legal representatives, authorized agents, children and parents * Chapters 10.15.1, 10.15.3, 10.15.4 and 10.15.5: Amendment of wordings and more precise description for time points of concomitant therapy and medication * Chapter 21.1: Addition of Figure 3 (Levels of activity of known corticosteroids for topical application) Chapter 22: Addition of reference for Stepien et al. 2022. | | |
| Is this amendment likely to have a substantial impact on the safety or rights of the participants? | | Not available. | |
| Is this amendment likely to have a substantial impact on the reliability and robustness of the data generated in the clinical trial? | | Not available. | |

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1. Protocol Summary
   1. Protocol Synopsis
      1. Primary and Secondary Objectives and Estimands

**Primary Objective and Endpoint**

Evaluation of the efficacy of deucravacitinib on objective clinical symptoms/ disease activity in lichen planus patients

* Change in the objective clinical symptoms (measured with the Lichen Planus Activity and Damage Index (LiPADI) Activity Score, from baseline (V1, day 1) to EOS (V4, day 112)

**Secondary Objectives and Endpoints**

1. To assess whether the administration of deucravacitinib in lichen planus patients is associated with reduced inflammatory parameters (from blood and skin samples) => mRNA-based gene expression analysis of IFN genes (CXCL10, CXCL9, CCL5, MxA, BLyS, TRAIL etc.)

* Change in the LiPADI Activity Score from baseline (V1) to V3, V4/OLE-V1, SC-1, SC-2, OLE-V2, SC-3 and OLE-V3 in both arms
* Differences in IFN gene expression profile (CXCL10, CXCL9, CCL5, MxA, BLyS, TRAIL etc.) in peripheral blood and skin (BOS/V1, EOS/V4, OLE-V3) between placebo- and treatment-arm
* Change in IFN gene expression profile (CXCL10, CXCL9, CCL5, MxA, BLyS, TRAIL etc.) in peripheral blood and skin (BOS/V1 vs EOS/V4 vs OLE-V3) in both arms

2. To assess whether the administration of deucravacitinib in lichen planus patients is associated with improvement of quality of life (Dermatological Quality of Live Index = DLQI, validated score)

* Change of DLQI from baseline (V1) to EOS (V4) between placebo- and treatment-arm
* Change of DLQI from baseline (V1) to V3, V4/OLE-V1, SC-1, SC-2, OLE-V2, SC-3, OLE-V3 in both arms

3. To assess whether the administration of deucravacitinib in lichen planus patients is associated with improvement of itching via the Numeric rating scale (NRS) for average itch during the past 24 hours

* Change of Itch NRS from baseline (V1) to EOS (V4) between placebo- and treatment-arm
* Change of Itch NRS from baseline (V1) to V3, V4/OLE-V1, SC-1, SC-2, OLE-V2, SC-3, OLE-V3 in both arms

4. To assess whether the administration of deucravacitinib in lichen planus patients is associated with improvement/reduction of the amount of steroids used

* Change in the amount of steroids used from baseline (V1) to EOS (V4) between placebo and treatment-a
  + 1. Overall Design

Key aspects of the trial design are summarised below.

|  |  |  |  |
| --- | --- | --- | --- |
| **Intervention Model:** | Randomized, double-blind | **Population Type:** | With disease |
| **Control Type:** | Placebo, Open-label extension | **Population Diagnosis or Condition:** | Symptomatic Lichen planus |
| **Control Description:** | Placebo | **Population Age:** | Minimum: 18 years of age Maximum: NA |
| **Intervention Assignment Method:** | Randomization | **Site Distribution and Geographic Scope:** | Germany |

**Number of Arms:** 2

**Trial Blind Schema:** Double Blind

**Blinded roles:** The following roles indicated will not be made aware of the treatment group assignment during the trial: Investigator, participant

**Number of Participants:**

It is planned to enroll a total a total number of 30 subjects in this trial with 2:1 randomization (20 subjects treated with deucravacitinib/verum; 10 subjects treated with placebo)

**Duration**

Duration of treatment: 16 weeks

Open-label extension: optional 32 weeks treatment with Deucravacitinib.

Per Subject:

* Duration of the double-blind trial phase: 16 weeks
* Total duration with optional open-label extension: 48 weeks
* Safety follow up: 30 days after last application of deucravacitinib

Trial duration:

* Planned total trial duration (incl. OLE): 24 months
* Planned total trial duration (incl. report & publication): 36 months
* Planned Recruiting Period: 11 months
* First subject in to last subject out without OLE: 16 months
* First subject in to last subject out with OLE: 24 months
* First subject first visit (FPFV/ FPI) = Start date: 01/Nov/2023
* Last subject last visit (LPLV/ LPO without OLE) = Planned end date of clinical study phase: 01/Mar/2025
* Planned End Date of open-label extension (LPLV/ LPO with OLE): 01/Dec/2025

**Committees:**

Independent Committees: Not applicable

* 1. Trial Schema

A diagram of a medical procedure

Description automatically generated

A screenshot of a computer screen

Description automatically generated

This is a prospective, phase II, national, multicenter, randomized, double-blind, 2-arm, parallel, placebo-controlled clinical trial. The double-blind phase of the trial (16 weeks) will be followed by an optional open-label extension phase (32 weeks).

* 1. Schedule of Activities

A medical report with a number of text

Description automatically generated with medium confidence

1 incl. prior therapies/ medications and concomitant medications

2 Handing out diary at Visit 1, return of diary at Safety FU

3 incl. resting systolic and diastolic blood pressure, pulse and temperature

4 Parameters in detail see 11.1.7

5 Parameters in detail see 11.1.7; incl. pregnancy test for women of childbearing potential

6 Numeric rating scale (NRS) for average itch during the past 24 hours

7 Photo documentation of skin condition is performed only in the site Bonn. Detail see 11.1.9.2

8 AEs may be reported spontaneously by the patient or discovered as a result of general non-directed questioning by the trial personnel or by physical examination. All AEs will be followed until the event resolves or stabilizes at a level acceptable to the investigator.

9Check of In-/Exclusion criteria, e.g. results of Screening Lab

10Intake of first tablet under supervision

11OLE = Open Label Extension

12Safety FU is only conducted after visit 4 when the subject does not continue with the Open Label Extension.

13Drug Dispensation is only conducted at visit 4 when the subject continues with the Open Label Extension.

A document with text on it

Description automatically generated

1incl. prior therapies/ medications and concomitant medications

2 Return of diary at Safety FU

3 incl. resting systolic and diastolic blood pressure, pulse and temperature

4 Parameters in detail see 11.1.7

5 Parameters in detail see 11.1.7; incl. pregnancy test for women of childbearing potential

6 Numeric rating scale (NRS) for average itch during the past 24 hours

7 Photo documentation is performed only in the site Bonn. Detail see 11.1.9.2

8 AEs may be reported spontaneously by the subject or discovered as a result of general non-directed questioning by the trial personnel or by physical examination. All AEs will be followed until the event resolves or stabilizes at a level acceptable to the investigator.

9 Open label extension starts with OLE-V1, which coincidences with V4 of the double-blind phase; for activities of OLE-V1 see “Activities for Double-Blind Trial Phase” (Visit 4=OLE-V1).

10 SC = Short check-up visits

>

1. Introduction
   1. Purpose of Trial

Deucravacitinib is a highly selective and potent inhibitor of the JAK family member TYK2 (Chimalakonda et al. 2021). TYK2 plays an important role in JAK-STAT-mediated signal transduction of various ligands, including IL-23, IL-12 and, in particular, type I IFN (Jo et al. 2022). Deucravacitinib has previously been tested as a treatment for adults with moderate-to-severe plaque psoriasis in large clinical trials offering promising results (Armstrong et al. 2022; Strober et al. 2022).

Lichen planus is a type I IFN-mediated inflammatory skin disease that can affect the mucous membranes as well as the skin and may represent a severe burden in patients' lives (Boch et al. 2021). Preliminary studies show that TYK2 is highly expressed in lichen planus skin lesions. Thus, selective TYK2 inhibitors may represent a promising therapeutic concept for lichen planus, but a controlled, double-blind clinical trial to support this hypothesis is missing.

5.1 Background

5.1.1 Scientific Rationale & Hypothesis

Lichen planus is a chronic inflammatory disease that affects the skin and/or mucous membranes. Lichen planus patients, especially those with oral manifestations in form of ulcers, can suffer from severe discomfort, itching and may experience a significant reduction in their quality of life. Despite the therapeutic need, no specific drug has been approved to date (Boch et al. 2021).

The disease is characterized by a typical histological pattern called interface dermatitis (ID), which is defined by the presence of necroptotic keratinocytes and an epitheliotropic cytotoxic lymphocytic infiltrate at the dermoepidermal junction (Sugerman et al. 2000).

Type-I-interferon (IFN) signaling plays a crucial role in inflammatory skin diseases featuring ID as these IFNs induce the expression of proinflammatory chemokines (e.g. CXCL9 and CXCL10) (Wenzel und Tüting 2008; Wenzel et al. 2006). The major pathway utilized by IFNs is the JAK-STAT pathway. Upon binding of type-IIFNs to their receptor, downstream JAK1 and TYK2 are activated and mediate IFN-associated proinflammatory gene expression. In LP, the expressed chemokines attract effector cells to lesional tissues that exert cytotoxic effects especially towards basal keratinocytes with subsequent cytokine release, leading to a continuous "self-recruitment" as a hallmark of chronic inflammation (Wenzel et al. 2006).

The described insights into the pathophysiological mechanisms underline the importance of the JAK1/TYK2- STAT pathway and its potential as a therapeutic target. TYK2-inhibitors aim to prevent JAK1/TYK2-/STATmediated signal transduction, thereby leading to reduced chemokine expression by a very unique way of allosteric inhibition of TYK2 - compared to other JAK-family-inhibitors - via binding to the regulatory domain. Due to this unique mechanism, potentially drug-limiting side effects could be prevented (Chimalakonda et al. 2021; Liu et al. 2021).

5.1.2 Deucravacitinib

According to BMS IB version 09 for deucravacitinib

Deucravacitinib is a potent, highly selective small molecule inhibitor of TYK2. TYK2 is a member of the JAK family and interacts with both JAK1 and JAK2 each as a dimer to ensure JAK-STAT mediated signal transduction of several ligands such as IL-23, IL-12, and type I IFN.

Unlike other inhibitors of JAK family members (JAK1/JAK2/JAK3), the selective TYK2 inhibitor deucravacitinib has a specific binding mechanism that accounts for its high selectivity over the other JAK family members. Deucravacitinib binds to the regulatory pseudokinase domain of TYK2 and stabilizes an inhibitory interaction between the pseudokinase and catalytic domains of the enzyme. This leads to blockade of receptor-mediated activation of TYK2 and consequent inhibition of downstream functions in cells and in vivo. The binding mode of deucravacitinib exploits the unique structural features of the TYK2 pseudokinase domain compared to other kinases and pseudokinases to achieve high biochemical and cellular functional selectivity. This approach distinguishes deucravacitinib from non-selective inhibitors of the JAK kinase family that target the highly conserved active site of the kinase domain.

The aims of our study are as follows:

* Deucravacitinib reduces the objective clinical symptoms/disease activity of lichen planus.
* Deucravacitinib alleviates the subjective symptoms of lichen planus and thus improves the quality of life of lichen planus patients.
* Deucravacitinib reduces the inflammatory signature in blood and skin samples from lichen planus patients (mRNA evaluation).
  1. Summary of Benefits and Risks
     1. Benefit Summary

Based on current clinical trial data, deucravacitinib is emerging as a promising treatment option for inflammatory dermatoses. In two large phase II and III trials in psoriasis vulgaris (POETYK-Pso I & POETYK-Pso II), deucravacitinib showed significant efficacy and good tolerability (Armstrong et al. 2022; Strober et al. 2022). In addition, TYK2 inhibitors feature a specific binding mechanism to the JAK enzyme that differs from that of other JAK inhibitors and is therefore considered particularly selective. Side effects currently observed with other JAK inhibitors have not been described for selective TYK2 inhibitors. TYK2 is known to mediate intracellular signal transduction of type-I-IFNs. Since lichen planus is a type-I-IFN-mediated disease and TYK2 is strongly expressed in lichen planus skin lesions, an efficacy of TYK2 inhibitors can be assumed - based on the described patho-physiological principles.

* + 1. Risk Summary and Mitigation Strategy

There are risks for patients in the form of side effects (described in detail in section 10.4). Patients will be informed in detail about these risks before consenting to participate in the study. Furthermore, the inclusion and exclusion criteria select patients to ensure that high-risk patients (e.g. patients with recurrent herpes zoster infections, immunodeficiency syndromes, severe liver failure) will not be enrolled in the study. In case of occurrence of side effects, we will take necessary adjustments immediately after reporting, such as observation, therapeutic recommendations or –adjustment, or discontinuation of the study medication.

* + 1. Overall Benefit:Risk Conclusion

Deucravacitinib is a TYK2 inhibiting small molecule approved by the FDA and – since March 2023 – also by the EMA for the treatment of Psoriasis vulgaris. Since there is evidence for an immunomodulating effect additionally to its unique binding mechanism deucravacitinib is currently under investigation as targeted therapy of several other diseases such as psoriatic arthritis, systemic lupus erythematosus and ulcerative colitis (NCT04613518) (Mease et al. 2022; Danese und Peyrin-Biroulet 2021; Morand et al. 2022). The described side effects (e.g., upper respiratory tract infections, herpes simplex, folliculitis) are most likely due to its immunosuppressive effect (antiviral immune response is mediated via type-I-IFN-induced TYK2/JAK1-signal transduction, which is inhibited by deucravacitinib). Lichen planus is a disease associated with severe impairment of life quality. Current therapeutic options are mostly based on empirical data (small studies, case reports) and are limited by side effects, decreasing efficacy, resistance, or restricted use, thus there is a great medical need for new therapeutic strategies. Based on the specific binding mechanism and recent data from previous studies, typical JAK inhibitor-related, potentially therapy-limiting side effects such as thrombocytopenia or anemia are not expected. Therefore, investigation of deucravacitinib in lichen planus patients under strict medical supervision as performed in the present study (in particular to intercept upcoming infections as soon as possible), seems to be justifiable. In conclusion, the overall assessment of the benefitrisk ratio in the DEUCRALIP study justifies the conduct of the present study.

1. Trial Objectives and Estimands
   1. Primary Objective(s) and Associated Estimand(s)

**Primary Objective and Endpoint**

Evaluation of the efficacy of deucravacitinib on objective clinical symptoms/ disease activity in lichen planus patients

* Change in the objective clinical symptoms (measured with the Lichen Planus Activity and Damage Index (LiPADI) Activity Score, from baseline (V1, day 1) to EOS (V4, day 112)
  1. Secondary Objective(s) and Associated Estimand(s)

**Secondary Objectives and Endpoints**

1. To assess whether the administration of deucravacitinib in lichen planus patients is associated with reduced inflammatory parameters (from blood and skin samples) => mRNA-based gene expression analysis of IFN genes (CXCL10, CXCL9, CCL5, MxA, BLyS, TRAIL etc.)

* Change in the LiPADI Activity Score from baseline (V1) to V3, V4/OLE-V1, SC-1, SC-2, OLE-V2, SC-3 and OLE-V3 in both arms
* Differences in IFN gene expression profile (CXCL10, CXCL9, CCL5, MxA, BLyS, TRAIL etc.) in peripheral blood and skin (BOS/V1, EOS/V4, OLE-V3) between placebo- and treatment-arm
* Change in IFN gene expression profile (CXCL10, CXCL9, CCL5, MxA, BLyS, TRAIL etc.) in peripheral blood and skin (BOS/V1 vs EOS/V4 vs OLE-V3) in both arms

2. To assess whether the administration of deucravacitinib in lichen planus patients is associated with improvement of quality of life (Dermatological Quality of Live Index = DLQI, validated score)

* Change of DLQI from baseline (V1) to EOS (V4) between placebo- and treatment-arm
* Change of DLQI from baseline (V1) to V3, V4/OLE-V1, SC-1, SC-2, OLE-V2, SC-3, OLE-V3 in both arms

3. To assess whether the administration of deucravacitinib in lichen planus patients is associated with improvement of itching via the Numeric rating scale (NRS) for average itch during the past 24 hours

* Change of Itch NRS from baseline (V1) to EOS (V4) between placebo- and treatment-arm
* Change of Itch NRS from baseline (V1) to V3, V4/OLE-V1, SC-1, SC-2, OLE-V2, SC-3, OLE-V3 in both arms

4. To assess whether the administration of deucravacitinib in lichen planus patients is associated with improvement/reduction of the amount of steroids used

* Change in the amount of steroids used from baseline (V1) to EOS (V4) between placebo and treatment-a
  1. Exploratory Objective(s)

Not applicable.

1. Trial Design
   1. Description of Trial Design

Trial Design This is a prospective, phase II, national, multicenter, randomized, double-blind, 2-arm, parallel, placebo-controlled clinical trial. The double-blind phase of the trial (16 weeks) will be followed by an optional open-label extension phase (32 weeks).

* + 1. Treatment Groups

In total 30 subjects with histologically proven and symptomatic lichen planus will be enrolled in this trial. 10 of these patients will be randomized into the placebo group, 20 will be randomized into the verum group. Treatment arm A - Deucravacitinib: 6 mg oral deucravacitinib once daily Treatment arm B - Placebo: oral matching placebo once daily A schedule of activities and flow chart are provided in the section 2.

* + 1. Trial Sites

The trial will be conducted in minimum three centers in Germany , which must meet the structural and personnel requirements for performing the planned regular trial-related investigations. If necessary, additional qualified centers may be included during the conduct of the trial.

* + 1. Number of Subjects

It is planned to enroll a total of 30 subjects in this trial. In order to enroll a sufficient number of subjects with lichen planus disease according to inclusion and exclusion criteria, screening of subjects will be performed. Subjects with lichen planus mucosal and/or skin lesions of both male and female gender will be included. Subjects will be randomized in a ratio of 2:1 as follows: 20 subjects will be randomized in treatment arm A – Deucravacitinib, oral once daily 10 subjects in treatment arm B – Placebo, oral once daily

* + 1. Time Schedule

Per Subject:

* Duration of the double-blind trial phase: 16 weeks
* Total duration with optional open-label extension: 48 weeks
* Safety follow up: 30 days after last application of deucravacitinib

Trial duration:

* Planned total trial duration (incl. OLE): 24 months
* Planned total trial duration (incl. report & publication): 36 months • Planned Recruiting Period: 11 months
* First subject in to last subject out without OLE: 16 months
* First subject in to last subject out with OLE: 24 months
* First subject first visit (FPFV/ FPI) = Start date: 01/Nov/2023
* Last subject last visit (LPLV/ LPO without OLE) = Planned end date of clinical study phase: 01/Mar/2025
* Planned End Date of open-label extension (LPLV/ LPO with OLE): 01/Dec/2023
  1. Rationale for Trial Design
     1. Rationale for Intervention Model

In our preliminary work, we found TYK2 to be strongly expressed in lichen planus skin lesions (predominantly in infiltrating immune cells and keratinocytes) compared to healthy controls (see Appendix 21.1 Figure 1). According to these findings, selective TYK2 inhibitors may represent a promising therapeutic concept for lichen planus. Positive results of this trial may improve therapeutic strategies for lichen planus patients.

This Study is concepted as double blinded study of deucravacitinib versus placebo (16 weeks), followed by an open label phase (all patients on deucravacitinib) for 32 weeks. The open label phase (all patients receive deucravacitinib) will help to recruit patients for this trial and provide long term safety and efficacy data in the target population.

* 1. Trial Stopping Rules

See Section 7.

* 1. Start of Trial and End of Trial

The regular end of trial is defined as last patient last visit (LPLV) of the double-blind Phase (day 112). After completion of the Open Label Extension Phase (OLE, day 336), the database-closure will be initiated and the end of the trial has been reached.

* 1. Access to Trial Intervention After End of Trial

No specific post-study arrangements are made and no specific post-study care will be performed after this study. All subjects will return to their standard medical care after the study, as needed. This also applies to subjects who withdraw their consent during the course of the study. An end-of-study visit and safety follow-up must be performed as described above.

1. Trial Population
   1. Description of Trial Population and Rationale

This trial can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions have to be taken into consideration when deciding whether this protocol is suitable for a particular subject.

All subjects ≥ 18 with histological proven and symptomatic lichen planus with mucosal and/or skin lesions of both female and male gender are eligible for inclusion in the trial.

* + 1. Gender Distribution

No gender ratio has been stipulated in this trial as the results of preclinical and / or clinical studies or medical literature and did not indicate any difference in the effect of the trial treatment in terms of efficacy and safety.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

* 1. Inclusion Criteria

Subjects will only be included in the study if they meet all of the following criteria:

General inclusion criteria:

1. Subjects male or female, aged ≥18 years
2. The patient has given written informed consent to participate in the trial
3. Subjects with histologically proven and symptomatic lichen planus
4. Ability to follow study instructions and willingness to attend and complete all required visits
5. LiPADI Activity Score ≥ 6 or ≥ 3 in patients with mucosal involvement only
   1. Exclusion Criteria

Subjects will not be included in the study if they meet all of the following criteria:

General exclusion criteria:

1. Subjects without legal capacity are unable to understand the nature, scope, significance and consequences of this clinical trial
2. Subjects with a physical or psychiatric condition which at the investigator’s discretion may put the subject at risk, may confound the trial results, or may interfere with the subject’s participation in this clinical trial
3. Reported history (within the last 12 months before screening) or persistent abuse of medication, drugs or alcohol in the assessment of the medical practitioner investigator, considering safety and trial and medication adherence of the participant
4. Known allergy/ incompatibility against deucravacitinib
5. Simultaneous participation in another clinical trial, or participation in a clinical trial taking an investigational product (except for DEUCRALIP/deucravacitinib in lichen planus), up to 120 days prior to participation in that clinical trial.

Indication specific exclusion criteria:

1. Subjects with a history of malignant neoplasm within the last 5 years with the exception of basal cell or squamous cell carcinoma of the skin treated with local resection only or carcinoma in situ of the uterine cervix treated locally and with no evidence of metastatic disease for 3 years
2. Chronic or acute infectious disease (including but not limited to HIV, Hepatitis B or C infection, Tbc or latent Tbc infection), disease predisposing for infectious disease or recurring infectious diseases in the history
3. Hospitalization for treatment of infection within 60 days prior to Day 1
4. History of serious herpes zoster or serious herpes simplex infection, which includes, but is not limited to, any episode of disseminated herpes simplex, multidermatomal herpes zoster, herpes encephalitis, ophthalmic herpes, or recurrent herpes zoster (recurrent is defined as 2 episodes within 2 years)
5. Subjects with a history of a primary immunodeficiency
6. Subjects with severe hepatic impairment (Child-Pugh C)
7. Subjects who never received a COVID-vaccination following EU regulations
8. Subjects who have never experienced a COVID-19 infection
9. Subjects who will need to receive a COVID-vaccination with an mRNA vaccine during the double-blind phase of the study
10. Subjects who will need to receive routine-vaccination during the study period (Comment: Lichen planus is an IFN-mediated inflammatory disease which is prone to worsen after application of vaccines, due to their IFN-stimulating effects)
11. Subjects with clinically significant abnormal laboratory value in the opinion of the investigator

Excluded concomitant medications:

1. Subjects treated within the last 8 weeks before baseline/day 1 with oral deucravacitinib or any other systemic JAK/TYK-specific inhibitor.
2. Subjects treated within the last 8 weeks before baseline /day 1 with any systemic immunosuppressive/ immunomodulatory agent, other than SOC-medications (for SOC-medications see chapter 10.15.3.)
3. Patient treated within the last 12 weeks before baseline/day 1 with any systemic retinoid
4. Subjects treated topically within the last 4 weeks before baseline/day 1 with a topical class III or class IV steroid (as shown in Figure 3) and/ or other topical immunosuppressive agents, other than SOCmedications (for SOC-medications see chapter 10.15.3.)

Exclusion criteria regarding special restrictions for females:

1. Women who are currently pregnant (positive pregnancy test, e.g. β-hCG test in urine/serum) or lactating women
2. Woman with a planned pregnancy within the study period and 16 weeks thereafter
3. Females of childbearing potential, who are not using and not willing to use medically reliable methods of contraception for the entire study duration and 16 weeks thereafter (such as oral, injectable, or implantable contraceptives, or intrauterine contraceptive devices) unless they are surgically sterilized/ hysterectomized or there are any other criteria considered sufficiently reliable by the investigator in individual cases.
   1. Contraception
      1. Definitions Related to Childbearing Potential

Not available.

* + 1. Contraception Requirements

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%. Therefore, these women must have a negative serum pregnancy test at screening, and agree to 1 of the following:

Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent (The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception).

**OR**

Consistent and correct use of 1 of the following acceptable highly effective methods (<1% failure rate) of birth control for 1 month prior to the start of the study agent, during the study, and 16 weeks after the last dose of study agent:

* Oral, intravaginal, or transdermal hormonal contraceptive, either combined (estrogen and progestogen containing) or progestogen alone
* Injectable, oral, or implantable progestogen
* Implants of levonorgestrel or etonogestrel
* Estrogenic vaginal ring
* Percutaneous contraceptive patches
* Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS) with < 1% failure rate as stated in the product label
* bilateral tubal occlusion
* Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, “documented” refers to the outcome of the investigator's/designee’s medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject’s medical records

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

Women of non-childbearing potential who do not require contraception during the study are defined as:

* Postmenopausal (defined as no menses for 12 months without an alternative medical cause)
* Permanently sterile (hysterectomy, bilateral salpingectomy, bilateral tubal occlusion / ligation procedures, and bilateral oophorectomy)

In addition, as a precaution, sexually active male patients or their partners are advised to use a reliable method of contraception during treatment of the male patient and for at least 16 weeks after discontinuation of deucravacitinib (having surgery where the tubes that carry sperm from your testicles are closed (vasectomy).

or complete abstinence). Men should not donate semen during therapy and for a period of 16 weeks after stopping deucravacitinib.

* 1. Lifestyle Restrictions

Not applicable.

* 1. Screen Failure and Rescreening
     1. Retesting

If in the Investigator’s judgement, the screening laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator’s rationale should be documented. Laboratory values can be retested during Screening provided that the patient can be evaluated for eligibility and randomized within the allowed Screening period.

* + 1. Rescreening

A subject who does not meet all study eligibility criteria due to a transient condition observed at Screening (e.g., prohibited medications that were subsequently discontinued) may be allowed to return for rescreening after consultation with the sponsor delegated person. The subject will be re-consented, and assent obtained (if applicable) if rescreening occurs outside of the 60-day screening window. In this case, all screening procedures must be repeated.

1. Trial Intervention And Concomitant Therapy
   1. Overview of Trial Interventions

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All relevant clinical and preclinical data and information about the substance is provided in the Deucravacitinib Investigator’s Brochure (IB) as well as in the simplified Investigator Medicinal Product Dossier (sIMPD).

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* 1. Description of Investigational Trial Intervention

Study drug includes both Investigational [Medicinal] Product (IP/ IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

* All products, active or placebo, being tested or used as a comparator in a clinical trial • Study required premedication, and
* Other drugs administered as part of the study that are critical to claims of efficacy (e.g., background therapy, rescue medications)
* Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection
  + 1. Authorization Statement

**For IMPs:**

* The IMP/ Placebo will be provided by the original manufacturer BMS to the sponsor free of charge and for the whole trial.
* The IMP deucravacitinib is used already a marketed product. It received its first approval (in the US on 9 September 2022) for the treatment of adults with moderate-to-severe plaque psoriasis who are eligible for systemic therapy or phototherapy. It was approved in Japan on 26 September 2022 for the treatment of plaque psoriasis, generalized pustular psoriasis and erythrodermic psoriasis. In March 2023, deucravacitinib received its approval for moderate to severe plaque psoriasis in adults in the EU by the EMA. Its trade name is SOTYKTU®.
* The IMP (test drug or comparator products) will not be modified from their usual commercial status.
* The IMP will be provided as tablets, identical to the approved preparation
* The IMP/ Placebo will be sent from BMS to the central pharmacy Leipzig at University Hospital Leipzig
* The IMP/ Placebo will be provided to the trial sites by the pharmacy Leipzig free of charge

**Auxiliary MP:** n.a.

* + 1. 10.4 Side Effects

*The following information is adapted from the U.S. prescribing information and the BMS investigators brochure(IB) Version 09 for deucravacitinib:*

The safety of deucravacitinib was evaluated in two placebo-controlled and active-controlled studies (PSO-1 and PSO-2) and in an open-label extension study involving subjects who completed PSO-1 or PSO-2. In these clinical trials, a total of 1,519 subjects with moderate-to-severe plaque psoriasis who were eligible for systemic therapy or phototherapy received deucravacitinib 6 mg orally once daily. Of these, 1,141 subjects received deucravacitinib for at least one year.

In studies PSO-1 and PSO-2, 1,681 subjects were randomized to receive deucravacitinib 6 mg (840 subjects), placebo (419 subjects), or apremilast 30 mg twice daily (422 subjects). All subjects randomized to placebo switched to deucravacitinib at week 16.

During the 16-week placebo-controlled period of the pooled clinical trials (PSO-1 and PSO-2), the number of treatment discontinuations due to adverse events was 2.4% in subjects treated with deucravacitinib, compared with 3.8% on placebo.

Table 1 summarizes the adverse events that occurred in at least 1% of subjects in the deucravacitinib group and at a higher rate than in the placebo group during the 16-week control period (adverse events that occurred in < 1% of subjects in the deucravacitinib group were herpes zoster).

**Table 1 (Adopted from the U.S. prescribing information and the BMS investigators brochure Version 09 for deucravacitinib): Adverse Reactions that Occurred in ≥ 1% of Subjects with Plaque Psoriasis in the deucravacitinib Group and More Frequently than in the Placebo Group in Trials PSO-1 and PSO-2 through Week 16**

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aIncludes upper respiratory tract infection (viral, bacterial, and unspecified), nasopharyngitis, pharyngitis (including viral, streptococcal, and unspecified), sinusitis (includes acute, viral, bacterial), rhinitis, rhinotracheitis, tracheitis, laryngitis, and tonsillitis (including bacterial, streptococcal)

bIncludes oral herpes, genital herpes, herpes simplex, and herpes virus infection

cIncludes mouth ulceration, aphthous ulcer, tongue ulceration, and stomatitis

dIncludes acne, acne cystic, and dermatitis acneiform

**Detailed and further information regarding specific Adverse Reactions (Adapted from the U.S. prescribing information and the BMS investigators brochure Version 09 for deucravacitinib**)

Infections

In the 16-week placebo-controlled period, infections occurred in 29% of the deucravacitinib group (116 events per 100 person-years) compared to 22% of the placebo group (83.7 events per 100 person-years). The majority of infections were non-serious and mild to moderate in severity and did not lead to discontinuation of deucravacitinib.

In the 16-week placebo-controlled period, serious infections were reported in 5 subjects (2.0 per 100 patient-years) treated with deucravacitinib, and 2 subjects (1.6 per 100 patient-years) treated with placebo. The most common serious infections reported during the 52-week treatment period were pneumonia and COVID-19.

Malignancies

During the 0-to-52-week treatment period of the two clinical trials, PSO-1 and PSO-2 (total exposure of 986 patient-years with deucravacitinib), malignancies (excluding non-melanoma skin cancer) were reported in 3 subjects treated with deucravacitinib (0.3 per 100 patient-years), including single cases each of breast cancer, hepatocellular carcinoma, and lymphoma after 24, 32, and 25 weeks of treatment, respectively. During PSO-1, PSO-2, and the open-label extension trial in which subjects who completed the controlled trials could enroll, a total of 3 subjects (0.1 per 100 patient-years), developed lymphoma while receiving deucravacitinib after 25, 77, and 98 weeks of treatment.

Laboratory Abnormalities

* Creatine Phosphokinase (CPK)

In the 16-week placebo-controlled period, increased CPK (including Grade 4) was reported in 23 subjects (9.3 per 100 patient-years) treated with deucravacitinib, and 5 subjects (4.1 per 100 patient years) treated with placebo.

* Liver Enzyme Elevations

Events of increases in liver enzymes ≥3 times the ULN were observed in subjects treated with deucravacitinib. In the 16-week placebo-controlled period the following elevation of liver enzymes were reported:

ALT elevations ≥3 times the ULN in 9 subjects (3.6 per 100 patient- years) treated with deucravacitinib, and 2 subjects (1.6 per 100 patient-years) treated with placebo.

AST elevations ≥3 times the ULN in 13 subjects (5.2 per 100 patient- years) treated with deucravacitinib, and 2 subjects (1.6 per 100 patient-years) treated with placebo.

* Decreased Glomerular Filtration Rate (GFR)

In the 16-week placebo-controlled period in subjects who had moderate renal impairment (eGFR 30-59 mL/min) at baseline, decreased GFR was reported in 4 subjects (1.6 per 100 patient-years) treated with Deucravacitinib, and 1 subject (0.8 per 100 patient-years) treated with placebo. Two of the deucravacitinib-treated subjects had worsening of baseline proteinuria. Nevertheless, no dose adjustment of the drug is required in case of impaired renal function.

* Lipid Elevations

Mean triglycerides increased by 10.3 mg/dL during the 16-week treatment period in subjects treated with deucravacitinib and by 9.1 mg/dL during the 52-week treatment period

Contraindications

Pregnancy

Available data from case reports on deucravacitinib use during pregnancy are insufficient to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Due to insufficient data, contraceptive methods must be adhered to throughout the study period (including OLE and some time thereafter) (sexual inactivity through abstinence or use of contraceptive methods with a failure rate of < 1%).

Lactation

There are no data on the presence of deucravacitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Deucravacitinib is present in rat milk. As the drug is present in animal milk, it is likely that the drug is also present in human milk. Therefore, patients who are breastfeeding must also not be included in the study.

Hepatic impairment

Deucravacitinib is not recommended for use in patients with severe hepatic impairment (Child-Pugh C). In patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, no dose adjustment of deucravacitinib is recommended.

* 1. Rationale for Investigational Trial Intervention Dose and Regimen

See other rationale sections.

* 1. Investigational Trial Intervention Administration

**Dosage and Dose Schedule:**

Eligible subjects will be randomized in a 2:1 ratio to receive either IMP or matching placebo.

For the first part of the trial (Double-blind Phase: V1-V4), the IMP (deucravacitinib) or placebo may be taken depending on group membership (either treatment-arm or placebo-arm).

For the second part of the trial (Open Label Phase: OLE-V1 – OLE-V3 including SC-visits), only IMP (deucravacitinib) will be taken.

Both the IMP and the placebo are intended to be taken orally, with or without food. No dose adjustment for deucravacitinib is needed. Contraindications for the use of deucravacitinib have to be considered.

The first intake takes place under supervision to control the intake technique and to detect possible administration mistakes or non-compliance at an early stage. Moreover, the patient gets a diary to reread all instructions and to document further information. Sell also 10.10.

Double-blind phase (V1-V4):

Deucravacitinib arm: 1 tablet (6 mg) once daily for 112 days

Placebo arm: 1 tablet once daily for 112 days

Open label phase:

1 tablet (6 mg) of deucravacitinib once daily 224 days

Tablets are dispensed to subjects in bottles at each visit.

Subjects have to present their bottles at each visit. The overdue tablets must be returned during the visits. The excessed tablets are returned at each visit and are counted. This ensures subjects do not have mistakenly any tablet - potentially placebo - left somewhere and are continuing on verum only.

* 1. Investigational Trial Intervention Dose Modification

Not applicable.

* 1. Management of Investigational Trial Intervention Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 12.5. for reporting details).

* 1. Preparation, Storage, Handling and Accountability of Investigational Trial Intervention(s)
     1. Preparation of Investigational Trial Intervention(s)

Not applicable.

* + 1. Storage and Handling of Investigational Trial Intervention
       1. Packaging and Labelling of IMP

The IMP/ Placebo will be manufactured and provided by BMS according to Good Manufacturing Practice and is responsible for the packaging and distribution of the IMP to the Pharmacy of University Hospital Leipzig.

GCP-conform labelling and blinding will be performed by the Pharmacy of the University Hospital Leipzig. The pharmacy will also distribute to the participating centers and organize that patients receive the correct treatment (IMP or placebo) according to the randomization result. For this reason, the pharmacy has access to the blinding tables generated by the randomization platform of the eCRF.

For details of packaging and the description of the label of the IMP refer to the IMP Manual which will be filed in the Trial Master File (TMF) and Investigator Site File (ISF)/ Pharmacy File. Sample of label according to CTR (EU) 536/2014 section VI will be provided separately.

* + - 1. Transport of IMP and Unauthorized AxIMP

The IMP will be provided by BMS to the central pharmacy.

Distribution of IMP to the trial sites is organized and managed by the central pharmacy Leipzig.

All further details concerning ordering and transport of the IMP to the pharmacy are described in further detail in the IMP Manual as well as Pharmacy manual of this trial which will be filed in the TMF, ISF and Pharmacy File.

**Auxiliary MP:** n.a.

* + - 1. Storage Requirements of IMP and Unauthorized AxIMP

The IMP(s) must be stored under the following conditions:

**IMP 1 – Deucravacitinib:** Stored in a tightly closed container (Bottles only) at 15° to 25°C (59° to 77°F), with protection from light.

**IMP 2 – Placebo:** Stored in a tightly closed container at 15° to 25°C (59° to 77°F), with protection from light.

The investigator will be responsible for ensuring the correct storage and sufficient stocks of the IMP(s) at the trial sites.

The investigator bears the responsibility for the proper storage in the original packaging according to the recommended storage conditions on the medication label in a secure location at the site, preferably in a lockable cabinet with restricted access to the investigator(s) and authorized site staff. Personnel who have access to the trial drug need to be listed (name and responsibilities) on the Authorization and Delegation Log in the trial specific Investigator Site File (ISF). A temperature monitoring of the IMPs is required.

The investigator should ensure that the IMP is only used according to the protocol.

Subjects should store the medication at home according to the recommended storage conditions on the medication label as instructed by the site personnel. Subjects will not maintain a temperature log.

The central pharmacy will be responsible for ensuring the correct storage and sufficient stocks of the IMP(s) at their facility.

The central pharmacy bears the responsibility for the proper storage in a secure location at the facility, preferably in a lockable cabinet with restricted access to the pharmacist(s) and authorized pharmacy staff. Personnel who have access to the trial drug need to be listed (name and responsibilities) on the Authorization and Delegation Log in the trial specific File/ Pharmacy File. A temperature monitoring of the IMP(s) is required.

**Auxiliary MP**: n.a

* + 1. Accountability of Investigational Trial Intervention

The study sites will be supplied by pharmacy Leipzig with sufficient IMPs by the Sponsor. The IMPs will be provided at temperature (15° to 25°C) not above 25° C (IMP 1) in validated transport boxes, see also 10.2 and 10.7. IMP must be received by a designated person (site or personal delegation log) at the trial site, handled and stored safely and properly in accordance with the environmental conditions (temperature, light and humidity) as determined by this protocol and in accordance with the IB and IMP manual, and kept in a secured location to which only the investigator and designated personnel has access.

The trial site maintains records to document receipt of the IMP, the stocks of IMP at the trial center, the dispense and use by the individual subject (drug accountability), the reconciliation, and the return of unused investigational medicinal products and their disposal on appropriate forms.

Verification of IMP accountability will be part of on-site monitoring activity. It is the responsibility of the investigator or the monitor (whoever first discovers it) to inform the sponsor delegated person or the coordinating investigator in case of deficiency regarding e.g. storage or accountability of the IMP.

It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

Drug dispensing and IMP management may occur via each participating trial site. They are responsible to ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by this protocol and in accordance with the IB.

If concerns regarding the quality, durability, reliability, safety, effectiveness, performance, tampering, diversion, and/or counterfeiting/falsification or appearance of the study drug arise, the study drug should not be dispensed and the sponsor should be contacted immediately by awareness. This includes all components co-packaged with the drug, such as drug containers and labelling.

In the event of a suspected product quality issue, the affected product must be quarantined immediately at the Investigational site or central pharmacy, depending where the problem is identified.

When reporting, as much product information as possible should be reported. At a minimum, but not limited to, include: Trial code, site number, impacted batch number, container/kit number(s), description of the problem, and any other supporting information. Further details the process are given in the IMP-Manual.

Investigational product documentation must be maintained including documentation of all processes required to ensure drug is accurately administered. This includes documentation of drug storage as well as storage temperatures, reconstitution, and drug return.

Ordering, receipt, dispense and destruction of IMP as well as the respective receipts therefore will be documented in the appropriate logs filed in the ISF.

It is the responsibility of the investigator or the monitor to inform the sponsor delegated person (SDP) or the coordinating investigator in case of deficiency regarding e.g. storage or accountability of the IMP. The monitor or the coordinating institution (Studienzentrale SZB) should be contacted immediately.

Copies of all forms completed at the trial site will be returned to the sponsor delegated person or the coordinating investigator at the end of the trial or will be collected by the monitor during the close out visit or have to be sent to the sponsor delegated person or the coordinating investigator on request.

The investigator may only dispense the investigational medicinal product to subjects who have signed the informed consent, who have been enrolled in the trial and have been randomized. The dispensing of the investigational medicinal product to subjects outside of this clinical trial is not permitted.

The investigator, or an individual who is designated by the investigator, should explain the correct use of the IMP to each subject and check at regular intervals that each subject is following the instructions correctly.

Further details about storage, handling and dispensing are given in the IMP-Manual.

Drug accountability for the IMP in the present trial will be performed. Documentation will be filed in the ISF and will be monitored by the clinical monitor of the trial.

* 1. Investigational Trial Intervention Assignment, Randomisation and Blinding
     1. Participant Assignment to Investigational Trial Intervention

Not Applicable.

* + 1. Randomisation

After the subject’s initial eligibility is confirmed and informed consent has been obtained, the subject will be enrolled into the study using the eCRF-System “MARVIN XClinical” to obtain the subject number. Every subject that signs or that has been signed for the informed consent form must be assigned a subject number. Specific instructions for randomization via the IWRS system (interactive web-based response system) will be provided to the investigational site in a separate document.

At V0 (screening) or V1 (Baseline, if not already occurred in screening phase) all subjects eligible for randomization will be randomly assigned in a 2:1 ratio to one of the following treatment groups:

Treatment arm A – Deucravacitinib: 20 subjects

Treatment arm B – Placebo: 10 subjects

The randomization will be stratified by trial site and localization of lesions: 1. skin lesions only, 2. skin lesions with oral involvement or oral lesions only.

The investigator or designee will randomize the subject according to the procedures established by the clinical study core unit. The following information is required for randomization:

* Date that informed consent was obtained
* Year of Birth
* Gender at birth
* Screening-ID
* Trial site
* Localization of lesions:
* 1. Skin lesions only
* 2. Skin lesions with oral involvement or oral lesions only

The randomization will be performed using block randomization and a stratification by center as well as localization of lesions: skin lesions with or without oral involvement.

After randomization the treatment can be initiated according to the randomization number. Between randomization and baseline must be at least 3 days for organizational issues.

The first dose of the study drug has to be administered within 4 weeks/28 days after screening.

The department of Biometry (IMBIE) will generate corresponding randomization and kit lists and the kits assignment with the chosen dose regimen will be performed by the eCRF system at each visit. The exact procedures for using the MARVIN XClinical System will be detailed in the manual.

* + - 1. Time of Inclusion into Clinical Trial

The individual participant is included into the trial at the time of randomization.

* + 1. Blinding

The first part of this trial is a double-blinded phase. The second phase is an open label phase. During the double-blinded phase, neither the subjects nor the investigator or sponsor will be aware of the treatment allocation unless in case of emergency (see the following chapter). Subjects assigned to one of the double-blinded treatments receive oral deucravacitinib or matching placebo. The tablets for oral use will be identical in appearance.

The IMP will be packed and delivered from BMS to the centers via central pharmacy. The IMP for each subject will be prepared by the central pharmacy. This will ensure double-blind conditions. The preparing sequence will be performed by the central pharmacy in accordance to the randomization list.

* + 1. Emergency Unblinding at the Site

Unblinding may be performed by the trial site using Emergency Codes which are provided to the trial site by the SZB as sealed Emergency Envelopes. These envelopes have to be stored at a location known and accessible to all study personnel. All study personnel have to be specifically trained in the code breaking procedures. Integrity of envelopes is controlled by the monitor.

The investigator should adhere to the randomization procedure of the clinical trial and ensure that the blinding code is only broken according to the protocol.

As a matter of principle, regular unblinding is only performed for interim analysis, after the last patient completed the double-blinded phase (Visit 4).

However, premature unblinding of a subject may be necessary in order not to jeopardise his/ her safety (ICH GCP 5.13.4). Any of the following situations may be reasons for premature unblinding:

* In emergency situations, if it is necessary for the subject subject's safety, i.e. if the further treatment depends on the knowledge of the investigational medicinal product.
* In the event of accidental administration of the investigational medicinal product to a person who is not a subject.
* In the event of the death of a subject, if a causal relationship between the treatment with the investigational medicinal product and death is suspected.
* In the event of SAEs/ SUSARs, under certain conditions (causal relationship with the investigational medicinal product).
* In emergency situations or in the event of accidental administration of the investigational medicinal product, the decision whether unblinding is necessary lies with the investigator. If possible, the coordinating PI should be consulted first.

Double-blind codes will not be broken for the purpose of clinical trial subjects gaining access to open label deucravacitinib.

In emergency situations or in the event of accidental administration of the IMP, the decision whether unblinding is necessary lies with the investigator. If possible, the SDP should be consulted first. In case of premature unblinding the investigator should inform the SDP as soon as possible.

Date and time of unblinding, name of the person who has broken the blind have to be documented on the respective emergency envelope. Any broken emergency envelope has to be filed in the Investigator Site File (ISF).

* 1. Investigational Trial Intervention Compliance

Treatment compliance will be monitored periodically by drug accountability as well as the subject’s medical record and eCRF.

Subjects are instructed at baseline visit to document any incident regarding the trial medication, such as a forgotten tablet or overdose, and provide a rationale for these events, if applicable. This documentation shall be done in a study diary, in which everything else relevant should also be recorded, such as AEs, medical consultations, surgeries, new medication, illness or other incidents. Study personnel should review subject’s documentation at each visit to confirm compliance with therapy.

They are instructed to place unused tablets/ handed out bottles and bring them along to the study site at each visit. The first intake takes place under supervision to control the intake technique and to detect possible administration mistakes or non-compliance at an early stage.

Unused tablets/ bottles will be returned to the study site at each visit.

* 1. Description of Non-Investigational Trial Intervention(s)
     1. Rescue Therapy

In case of an anaphylactic reaction ≥ grade 1: prompt intravenous application of prednisolone 250-500 mg plus H1-/H2-antihistamines, vasopressors if applicable. Subsequent constant clinical observation of vital signs for at least 5 hours, up to at least 24 hours depending on the specific grade/severity.

* 1. Concomitant Therapy

Any concomitant therapy and concomitant medication of a subject should be carried out during the clinical trial in consultation with the (principal) investigator. The concomitant medication is documented in the patient file and in the CRF.

* + 1. Previous/PrecedingTherapy/Medication of Trial Specific Illness

All previous treatments for managing the trial specific illness and applied medications will be documented in the CRF.

* + 1. Previous Therapy/Medication of Other Indications than the Trial Specific Illness

All previous treatments and medications for other indications than the trial specific illness occurred within the last 12 months before starting the trial will be documented in the CRF.

* + 1. Concomitant Therapy/Medication for Trial Specific Illness

It is allowed to treat the subject for its illness with following “standard of care (SOC)” treatment as follows:

1. Antimalarials (hydroxychloroquine only, maximum 200mg/day), which the subject has been taking for at least 8 weeks before baseline/day 1.
2. Oral Corticosteroids (maximum 5 mg Prednisone-equivalent per day), which the subject has been taking for at least 8 weeks before baseline/day 1.
3. Oral Antihistamines can be taken as always.
4. Subjects can also be treated with topical corticosteroids (maximum: use of a class II steroid 2x per day), lesional application only, which the subject has been using for at least 4 weeks before baseline/day 1 (as shown in Figure 3).
5. Topical calcineurin inhibitors (maximum 2x per day), lesional application only, which the subject has been using for at least 4 weeks before baseline/day 1.

All concomitant therapy or medication including their exact dosage, type and time of intake needs to be documented in the subjects’ medical record and in the appropriate eCRF.

* + 1. Concomitant Therapy/Medication for Other Indications

All concomitant therapies/medications other than the trial therapy/investigational medicinal product applied overlapping with IMP therapy or begun during the trial or during IMP administration at the discretion of the investigator will be documented in the subject’s medical record and in the appropriate eCRF

* + 1. Prohibited Concomitant Therapy

The following therapies / medications are not allowed to be applied overlapping with IMP therapy or begun during the trial or during IMP administration:

* Subjects treated within the last 8 weeks before baseline/day 1 with oral deucravacitinib or any other systemic JAK/TYK-specific inhibitor.
* Subjects treated within the last 8 weeks before baseline /day 1 with any systemic immunosuppressive/ immunomodulatory agent other than in the above listed SOC-medications (see chapter 10.15.3).
* Subjects treated within the last 12 weeks before baseline/day 1 with any systemic retinoid. Confidential EU trial No: 2022-502991-21-00 Clinical Trial Protocol version 3.0 of 07-NOV-2023 Page 47 of 88
* Subjects treated topically within the last 4 weeks before baseline/day 1 with a topical class III or class IV steroid (as shown in Figure 3) and/ or other topical immunosuppressive agents other than in the above listed SOC-medications (see chapter 10.15.3).

Every effort should be made to avoid the use of any of the listed prohibited therapies/medications during the entire of the trial.

1. Participant Discontinuation of Trial Intervention and Discontinuation or Withdrawal From trial
   1. Discontinuation of Trial Intervention for Individual Participants
      1. Permanent Discontinuation of Trial Intervention

A discontinuation or missed dose from the study treatment refers to any participant who does not receive the IMP for 72 consecutive hours. A participant discontinued from the study treatment may not necessarily be discontinued from the study as further study procedures or follow-up may be performed (safety), if planned in the study protocol. The Investigator should make all efforts to ensure that the participants remain in the study to ensure a proper safety follow-up and medical care if needed and document the reason for participant discontinuation of study treatment.

Information relative to premature discontinuation of the study drug will be documented (primary reason) in the eCRF. The Investigator will document which of the following reasons was responsible for discontinuation of study drug:

* AE (incl. SAE)
* Death
* Significant violation of the protocol
* Non-adherence to treatment regimen
* Physician Decision
* Pregnancy
* Other reason (non-AE)
* Lost to follow-up
* Withdrawal of Consent by Participant
* Trail Termination by Sponsor
* Other (specify)

Subjects who are pregnant will be discontinued from study drug dosing immediately (see Section 12.6 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

Subjects who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of the Schedules of Assessments including different options for follow-up and collection of data (eg, in person, by phone, by mail, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and AEs, and must document this decision in the patient’s medical records.

If a patient discontinues dosing due to an AE, including SAEs, the event should be followed as described in Section 12.1.

If a dose is missed by a subject, it must be taken as soon as possible and the investigator has to be contacted. If the dose is interrupted either by the subject for 72 consecutive hours, the subject must be excluded from the study. If the dose is interrupted for a shorter period of time (less than 72 consecutive hours), the study can be continued. If the dose is interrupted at several intervals for less than 72 consecutive hours, it is at the discretion of the investigator to decide whether the subject must be excluded from or can continue the study. An investigator can temporarily interrupt dosing for up to a maximum of 72 consecutive hours for a subject, for safety reasons or while monitoring abnormal laboratory tests if the investigator judges that this is necessary. The investigator should use their judgement with regard to unscheduled visits/laboratory/clinical assessments required to monitor the subject during this timeframe. If within this timeframe the investigator judges that it is safe to restart dosing, then the subject may restart investigational product. If the investigator judges that it is not safe to restart dosing within this timeframe then the subject must be permanently discontinued from treatment, have an EOS visit and enter the safety follow-up period.

If the study was not terminated by the subject or by the investigator due to protocol violations by the subject (e.g. lack of compliance), the patient can participate in the study a second time. This is particularly the case if the study was interrupted due to safety issues such as infections, including but not limited to COVID-19. As soon as it is foreseeable that the inclusion and exclusion criteria will be met again (e.g. last intake of deucravacitinib longer than 8 weeks prior to study inclusion/day 1), a new screening can be scheduled for the subject. If the inclusion and exclusion criteria are met, the subject can be re-enrolled in the study.

Participants who are randomized to treatment but do not receive the first study drug on the same day will be permitted to return for the first IMP administration on Day 1 if within the 28-day screening window. Participants who are randomized to treatment but do not receive the first study drug will be discontinued from study treatment and the study, with the exception of any participant being followed for an SAE.

* + 1. Temporary Discontinuation of Trial Intervention

See Section 7.1.1 above.

* + 1. Rechallenge

Not applicable.

* 1. Discontinuation or Withdrawal from the Trial
     1. Termination of the Trial for Individual Subjects

If the clinical trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the subject subjects and ensure appropriate therapy and follow-up for the subjects.

Where required by the applicable regulatory requirements, the competent authority(ies) and the ethics committee(s) will also be informed (this is usually done by the sponsor).

Details of the criteria for premature termination can be found below.

All participating subjects who are excluded prematurely from the study should be followed up 30 days after last intake of the medication. The Safety Follow-up visit is described in section 11.2.5.

* + 1. Termination/Withdrawal by the Subject

Subjects may withdraw from the trial at any time at their own request without stating the reason(s) for withdrawal. They will experience no disadvantage as a result of this decision and no alternative therapy will be withheld by the investigator.

In this case the investigator is urged to ask the subject to return for an early termination visit and to document information as much as possible in the CRF.

Reason, time point, and specific reason for premature study termination of each subject will be documented. The investigator should determine a primary reason for premature study termination of each subject. All relevant safety data until subject’s study termination will be collected and reported.

Whenever a subject is withdrawn from the trial, the circumstances of the withdrawal or discontinuation have to be recorded in detail in the eCRF and a complete final examination as scheduled for the termination visit should be conducted.

* + 1. Termination by the Investigator

Subjects can also be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons, e.g.:

* If the dose of IMP is forgotten for 72 consecutive hours (see chapter 10.11)
* Occurrence of intolerable adverse events and which would constitute an unacceptable high risk for the subject
* Lack of efficacy
* Hypersensitivity reactions ≥ Grade 2
* New diagnosis of hepatitis B/C, HIV, Tbc
* Medically indicated e.g. because it is found that inclusion/ exclusion criteria were violated
* Continuation is unacceptable because risks outweigh the benefits
* Pregnancy
* Significant protocol violations
* Non-compliance/Lack of compliance of the subject (e.g. taking prohibited medication)
* Life threatening infection
* Logistical reasons (e.g. subject changes his/her doctor or hospital or moves to another location)
* Any laboratory abnormality attached to life-threatening consequences (urgent treatment indicated)

Whenever a subject is withdrawn from the trial, the circumstances of the withdrawal or discontinuation have to be recorded in detail in the CRF and a complete final examination as scheduled for the termination visit should be conducted.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject.

In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal. The subject has to be requested to return all unused investigational product(s), if applicable, and followed-up regarding any unresolved adverse events.

* + 1. Termination of One of the Treatment Arms / or the Entire Trial

The sponsor/coordinating investigator is under obligation to monitor the progress of the clinical trial with regard to safety-relevant developments and, if necessary, initiate the premature termination of a treatment arm or the entire clinical trial.

The sponsor/coordinating investigator will be supported in this responsibility by a data monitoring safety committee, if applicable and if necessary.

A treatment arm or the entire clinical trial must be terminated prematurely if:

* New toxicological or pharmacological information about the IMP or SAEs invalidate the earlier benefit-to-risk ratio for the subject.
* Adverse events occurring in such severity and frequency that the proposed schedule can no longer be adhered to.
* The sponsor/coordinating investigator considers that the termination of the trial is necessary.
* Indications arise that the subjects' safety is no longer guaranteed,
* The questions addressed in the trial can be clearly answered on the basis of an interim analysis,
* An insufficient recruitment rate makes a successful conclusion of the clinical trial appear impossible or can be clearly answered on the basis of an interim analysis.

The reasons for such a decision should be documented in written form.

* + 1. Termination of the Trial in Individual Sites

Both the investigator and the sponsor/sponsor delegated person have the right to terminate the trial at one of the centers at any time for instances:

* Unforeseeable circumstances have arisen at the trial center concerned what preclude the continuation of the clinical trial.
* The investigator considers that the resources for continuation are no longer available.
* The investigator considers that the continuation of the trial is no longer ethically or medically justifiable.
* Subject recruitment is inadequate.
* Serious problems arise with regard to the quality of the collected data which cannot be resolved.
* Withdrawal of the opinion of the EC and/or regulatory authority.

Premature termination at one of the trial centers does not automatically mean a termination of already enrolled trail subjects. A separate decision on further treatment must be made for each subject, depending on the overall situation. So, it has to be clarified that:

* An adequate further treatment and follow-up of already enrolled subjects must be ensured.
* The documentation of already enrolled subjects will be reviewed for completeness and plausibility. Queries may be raised for further clarification before the center is closed. These queries must be answered properly by the center.
* The competent authority(ies) and ethics committee(s) must be duly notified of the center's closure, including reasons, within the specified period(s).
* The trial center concerned will be closed in stages by the CRA when a decision has been made on the further treatment of the subjects concerned.
  1. Lost to Follow-Up

A subject will be considered lost to follow-up (LTFU) if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a patient misses a required study visit:

• The site must attempt to contact the participant inquire about the reason for discontinuation/withdrawal, and follow up with any unresolved AEs/ SAEs and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

• Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the participant’s last known mailing address or local equivalent methods). These contact attempts should be documented in the participant’s medical record.

• Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

• A participant should not be considered LTFU until due diligence has been completed. Date of withdrawal/LTFU should be the date of last contact with the participant where safety status of the participant was assessed (e.g., study visit, dates of telephone calls and registered letters).

Discontinuation of a study or of the study as a whole are handled as part of 10.1

* 1. Regular End of the Trial

The regular end of trial is defined as last patient last visit (LPLV) of the double-blind Phase (day 112).

After completion of the Open Label Extension Phase (OLE, day 336), the database-closure will be initiated and the end of the trial has been reached.

To allow the study to be closed, all subjects planned to be enrolled must have permanently discontinued protocol treatment and must have a complete CRF documentation.

Study closeout visits will be performed to ensure that all open queries can be resolved and closed. During these visits, the monitors will ensure that the investigator’s regulatory files are up to date and complete and that any outstanding issues from previous visits have been resolved.

See the time schedule in section 8.5.

1. Trial Assessments and Procedures
   1. Trial Assessments and Procedures Considerations

The following section will give an overview and adequate explanations to the examinations and procedures to be performed in this trial and will be determined according to the time schedule given in section 8.5.

* 1. Screening/Baseline Assessments and Procedures
     1. Informed Consent

See section to 9.5.3

* + 1. Demographics

The following data will be recorded in the patient file and transferred to the eCRF:

* year of birth
* age (will be calculated in eCRF)
* sex/ gender
  + 1. Medical History / Concomitant Medication

The medical history and Concomitant Medication will be conducted at the screening visit (before randomization) and will include past and current conditions, treatments, surgeries and current medication, as documented in the doctoral letter and the hospital documentation system (ORBIS).

* + 1. Height, Weight, BMI

The subject will wear lightweight clothing and no shoes during weighing.

Height will be recorded in centimeters (cm); the subject will not wear shoes.

Weight will be recorded in kg and may be re-measured at any time during the trial at the discretion of the investigator.

The body-mass-index (BMI) will be calculated automatically in the eCRF from the entries for measured height and weight.

* 1. Efficacy Assessments and Procedures
     1. Questionnaires

**LiPADI (Lichen Planus Activity and Damage Index):** the LiPADI is designed to assess the severity of Lichen planus skin, mucosal, and nail lesions as well as hair loss/scaring alopecia to provide an integrative scoring for LP activity and damage caused by the disease. Skin lesions are assessed in nine locations: scalp, face, chest, abdomen, back and buttocks, arms, hands, legs, and feet. The characterization of lesion activity included erythema, hypertrophy, and scaling, while the damage was reflected by the assessment of hyperpigmentation and scaring/atrophy. In addition, mucosal lesions, nail lesions, hair loss, and scarring alopecia are determined as well. In this study we will use the disease activity parameters of this score (LiPADI Activity Score), which includes disease activity parameters for cutaneous lesions, mucous membrane lesions and nail lesions. The following parameters are collected for this index: Overall Activity score. See Appendix 21.1 Figure 2.

**Itch-NRS (Itch-Numeric rating scale):** for average itch during the past 24 hours. In this unidimensional scale for itch intensity measurement subjects are asked to assign an average numerical score on a scale from 0 to 10, with 0 for having no itch and 10 having worst imaginable itch within the past 24 hours before survey. It represents high reliability and concurrent validity and is a popular score for all subjects due to its simple and time-saving format.

The following parameters are collected for the questionnaire: Average itch intensity within the past 24 hours before survey

**DLQI (Dermatology Life Quality Index):** A dermatology-specific Quality of Life instrument. It is a validated 10-question questionnaire that has been used in over 40 different skin conditions in over 80 countries and is available in over 90 languages. The questionnaire features 10 questions on the following topics: Symptoms, shame, shopping and home care, clothing, social and recreational activities, sports, work or study, close relationships, sex, treatment. Each question refers to the impact of the skin disease on the patient's life in the last 7 days.

The following parameters are collected for the questionnaire: Overall score

The handling of missing data will be done by using specified scoring manual and will be further explained in the statistical analysis plan.

* + 1. Photographic Documentation of Skin Condition

Photo documentation is performed only in the trial site Bonn.

At each visit at site Bonn, a whole-body-photograph is to be taken from the front and from the back, respectively. Skin condition is to be documented from a standardized distance of 2 meters with a predefined photo camera (e.g. Canon PowerShot SX60 HS). Underpants/panties and bra may be kept on. If necessary, more detailed images of the affected areas can be taken (e.g. if the lesions are confined to a specific area, such as the forearms).

Instructions for photo documentation can be found in lab manual which will be filed in the Investigator Site File.

* 1. Safety Assessments and Procedures
     1. Physical Examination

The physical examination (excluding genital/ rectal exam) will consist of an examination of the following:

general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, and extremities.

The physical examination performed on screening and/ or baseline prior to the first dose will serve as the baseline physical examination for clinical assessment. Any significant physical examination findings after dosing will be recorded as adverse events. A symptom-directed physical examination will be performed when necessary.

Thorough physical examination is to be performed according to the schedule of activities, relevant findings concerning these examinations will be documented in the eCRF.

If clinically significant findings (regarding physical examination, vital signs and weight), as determined by the Investigator, are recorded for a particular symptom, sign or abnormal measurement, that measurement will be repeated at medically appropriate intervals until the value returns to an acceptable range, a specific diagnosis is established, or the condition is otherwise explained.

* + 1. Vital Signs

Vital Signs include the following parameters:

* Body temperature (°C) at every visit to exclude pyrexia
* Blood pressure (mmHg) and heart rate (Beats per minute (bpm)): resting systolic and diastolic blood pressure and resting pulse after at least 5 minutes of rest will be measured at every visit.

Vital Signs have to be checked according to the schedule of activities and will be documented in the eCRF

* + 1. Clinical Laboratory Assessments

Laboratory tests to determine serum chemistry, hematology tests will be performed at the Laboratory of the treating University Medical Center laboratory of each participating center. Laboratory tests taken between the visits outside the center will be reviewed by the investigator. Any clinically relevant changes occurring during the study must be reassessed in the University Medical Center Laboratory, assessed for identification of AEs by the investigator and recorded, if applicable, in the adverse event section of the CRF.

After analysis, the samples will be destroyed locally.

The following parameters will be determined according to visit schedule (see section 2): Screening Laboratory (SLab):

* + Hepatitis Serology (immunoassays for Hepatitis B surface antigen and Hepatitis C antibodies) from serum
  + HIV test (combi-immunoassay for HIV 1 and 2 antibodies and p24 antigen) from serum
  + Blood test for tuberculosis (e.g. QuantiFERON-TB Gold (QFT) Assay) from whole blood
  + Routine Laboratory (RLab, as described below)

Required amount for Hepatitis/HIV serology serum sample: 5 mL of total blood.

Required amount for RLab serum sample: 5 mL of total blood.

Required amount for EDTA blood sample: 5 mL of total blood.

Required amount for QFT blood sample: 4 ml of total blood.

In total, for SLab 19 ml of total blood are required.

Routine Laboratory (RLab = BSC + CBC):

*Blood serum chemistry (BSC):*

* Sodium (Na)
* Potassium (K)
* Creatinine
* Creatine kinase (CK)
* Estimated glomerular filtration rate (eGFR)
* Bilirubin • Alkaline phosphatase (AP)
* Alanine aminotransferase (ALT/ GPT)
* Aspartate aminotransferase (AST/ GOT)
* Lipase
* Triglycerides (TG)
* Pregnancy test/β-hCG

*Complete Blood Count (CBC):*

* Leukocytes
* Neutrophils
* Lymphocytes
* Monocytes
* Eosinophils
* Basophils
* Hemoglobin
* Hematocrit (HCT)
* Mean corpuscular volume (MCV)
* Mean corpuscular hemoglobin concentration (MCHC)
* Platelets

Required amount for BSC serum sample: 5 mL of total blood.

Required amount for CBC EDTA blood sample: 5 mL of total blood.

In total, for RLab 10 ml of total blood are required per visit.

All clinically significant findings will be documented in the source data and in the eCRF as adverse events. Clinically significant findings at baseline visit which describe the baseline status of the subjects will be documented as concomitant disease under medical history.

Laboratory for mRNA-based Gene expression analyses of peripheral blood

These special laboratory tests are carried out during the study phase at V1 and V4 as well as at OLE-V3 of the open-label extension phase. 2.5 mL of peripheral blood will be collected in PAXgene tubes and later processed for gene expression analyses. Expression profiles before and after treatment will be compared in the different treatment arms. Amongst others, an interferon-score will be collected. This score includes the following parameters: IFN-Signature Score (gene-expression count of CLE-typical selected type-I/III-IFN-regulated genes, e.g. CXCL10, CXCL9, CCL5, MxA, BLyS, TRAIL etc.). Further parameters may be included at the discretion of the investigator.

These laboratory tests, which are collected at all centers, are evaluated centrally at the NGS Core Facility in Bonn.

Required amount for PAXgene blood sample: 2.5 mL of total blood.

A subject performing only the double blind trial phase has to spend approximately 74 ml of total blood throughout the trial (minimum 149 days).

A subject additionally performing the OLE phase has to spend approximately 126.5 ml of total blood throughout the trial (minimum 373 days).

* + 1. Pregnancy Testing

For all females of child-bearing potential, pregnancy testing will be performed at screening and every visit of the clinical trial, so that a non-pregnancy at the time of administration of study drug will be ensured.

Pregnancy testing for women of childbearing potential (WCBP) and results prior to each dosing

* Urine or serum pregnancy testing acceptable
* Timing of pregnancy test must be < 7 days prior to first dose

Pregnancy testing is a part of the RLab.

* + 1. Skin Sampling

Skin samples will be obtained via tape stripping at BOS/V1, EOS/V4 and OLE-V3 of all patients at two - at BOS/V1 defined and constantly used - areas of patient’s skin, one area will be lesional skin, the other one will be non-lesional skin. Skin stripping is a simple and non-invasive technique to study the immunological micro-environment of the uppermost skin layer, the stratum corneum. We intend to perform mRNA-based gene expression analysis of IFN genes (CXCL10, CXCL9, CCL5, MxA, BLyS, TRAIL, etc.) on the collected samples in addition to mRNA-based gene expression analysis of the corresponding IFN genes from peripheral blood.

* + - 1. Rationale

This technique is increasingly used in dermatological research, particularly in inflammatory skin diseases such as atopic dermatitis and psoriasis. For instance, most recently, Tsoi et al. compared skin tapes with whole skin biopsies from psoriasis patients with and without skin lesions, as well as healthy controls. The group found that transcriptomic profiling of RNA isolated from taped, lesional psoriatic skin efficiently captured genes expressed in the upper layers of the epidermis and accurately detected active immunologic pathways in psoriasis compared with whole skin biopsies. They concluded that tape stripping, as a less invasive and safer method for measuring transcriptomic changes in inflamed skin, offers the opportunity to extend studies of pathomechanisms and biomarkers in skin to much larger patient cohorts than has previously been possible.

* + - 1. Method

The tape is applied to cleansed skin at a defined area, pressed firmly with a pressure device for 5-15 seconds, removed with forceps or gloved fingers and stored in a vial with the adhesive side facing inward. Keurentjes et al. describe a protocol of tape stripping method. RNA isolation of the samples and transcriptome sequencing are conducted with standardized protocols.

* 1. Pharmacokinetics

Not applicable.

* 1. Biomarkers
     1. Genetics and Pharmacogenomics

Not applicable.

* + 1. Pharmacodynamic Biomarkers

Not applicable.

* 1. Immunogenicity Assessments

Not applicable.

* 1. Medical Resource Utilisation and Health Economics

Not applicable.

1. Adverse Events, Serious Adverse Events, Product Complaints, Pregnancy and Postpartum Information
   1. Definitions
      1. Definitions of Adverse Events

Adverse event means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

A subject means an individual who participates in a clinical trial, either as recipient of an investigational medicinal product (IMP) or as a control.

An IMP is a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.

An AE can be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational medicinal product, whether or not considered related to the investigational medicinal product.

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

* + 1. Definitions of Serious Adverse Events

A serious adverse event or reaction is any untoward medical occurrence that, at any dose:

* Results in death
* Is life-threatening
* Requires inpatient hospitalization
* on or prolongation of existing hospitalization
* Results in persistent or significant disability or incapacity, or
* Results in a congenital anomaly or birth defect,
* another, according to medical assessment, clinically relevant event.
* 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 has been more severe
* In general, ‘hospitalization’ signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious
* In-patient stays without an underlying adverse event are not SAE (e.g.: elective in-patient treatment due to a pre-existing condition; inpatient admission for social reasons; admission to a rehabilitation clinic or hospice)
* The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse, or potential DILI event as defined at 12.5.1.

* + 1. Adverse (Drug) Reaction (AR)

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase „responses to a medicinal product“ means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

* + 1. Unexpected Adverse (Drug) Reaction (UAR)

An adverse reaction, in which the nature or severity of the event is not consistent with the applicable reference safety information (e.g., Investigator's Brochure for an unapproved investigational medicinal product or package insert/summary of product characteristics for an approved product)Timing and Mechanism for Collection and Reporting

* + 1. Suspected Unexpected Serious Adverse (Drug) Reaction (SUSAR)

A SUSAR is an adverse reaction, which is suspected, serious and unexpected because the nature, severity or outcome of this event is not consistent with the applicable reference safety information (e.g. Summary of Product Characteristics for an authorized product or Investigator’s Brochures for an unauthorized investigational medicinal product)

* 1. Timing and Mechanism for Collection and Reporting

Safety data collection, documentation and reporting of adverse events will be performed according to the applicable laws and regulations (CTR, AMG, ICH GCP).

Details regarding safety data documentation and reporting are specified in the Safety Management Plan (SMP) of this trial. The Investigator's Brochure for an unapproved investigational product or summary of product characteristics for an approved product will be used as reference documents referring to safety specifications.

The investigator will be provided with AE and SAE reporting forms by SZB and will receive training for AE/ SAE definition, documentation and reporting. The AE/SAE documentation and reporting will be monitored on site.

* 1. Identification, Recording and Follow-Up
     1. Identification
        1. Criteria to be Evaluated by the investigator (1st assessment)

By including the patient in the clinical trial and first administration of IMP, all adverse events (AEs), including intercurrent diseases, must be documented in the patient file and subsequently in the CRF. Disease signs, symptoms and laboratory changes should, as far as possible, be combined into one single diagnosis. The documentation of the event shall include the following criteria: "type", "beginning and end" and "outcome of the event" (recovered, improved, unchanged, recovered with sequelae, worsened death, unknown). The adverse event is then evaluated by a physician according to the following criteria:

* + - 1. Criteria to be Evaluated by the Sponsor for SAEs (2nd assessment)

To take into account safety data available to the sponsor but not to the investigator at the time an SAE was detected, in addition to the initial assessment of a serious adverse event by the investigator, a second assessment of the event by the sponsor in terms of causality and probability of occurrence ("expectedness") and a continuous benefit-risk assessment are performed.

* **Causality:** If no information on causality is available from the investigator rapporteur, the sponsor should consult the investigator rapporteur and ask him to comment on this aspect. The sponsor cannot not downgrade the investigator's assessment of causality. If the sponsor disagrees with the investigator on the causal link, the report should include the opinion of both the investigator and the sponsor.
* **Expectedness**: Whether a serious adverse reaction is to be expected is assessed using the reference safety information (RSI). If the rapporteur investigator has provided information on whether an event is expected, the sponsor should take this into account
  + 1. Severity
       1. Assessment of Intensity

An assessment of intensity grade will be made using the general categorical descriptors outlined in the WHO Toxicity Grading Scale (see Table below). The investigator should use clinical judgment in assessing the severity of adverse events not directly experienced by the subject (e. g, laboratory abnormalities).

MILD Does not interfere with subject's usual function, easily tolerated.

MODERATE Interferes to some extent with subject's usual function.

SEVERE Interferes significantly with subject's usual function, incapacitating with inability to work or carry out usual activity.

* + - 1. Assessment of Seriousness (AE vs. SAE)

Determination of the seriousness of the adverse event according to the definitions for a serious adverse event (SAE) given in section 12.1

* + 1. Causality

Determination of the relationship of the adverse events to the medicinal product(s) being studied after having evaluated all accessible data according to the following classification:

**Suspected relationship (related):**

The temporal relationship between the adverse event and the administration of the IMP makes a **causal relationship possible, probable, or definite,** or other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

**No suspected relationship (not related):**

The temporal relationship between the adverse event and the administration of the IMP makes a **causal relationship unlikely or impossible (i.e. not related),** or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

When the final causality assessment is unknown and it is uncertain whether or not the investigational product caused the event, then the event should be handled as an SAE related (suspected) to the investigational product for reporting purposes.

The evaluation should consider nature and pattern of the reaction, temporal relationship to study medication, the clinical status of the patient, the concomitant medication and other relevant parameters. If the investigator believes that the SAE is not related to the investigational product but is potentially related to the conditions of the study the relationship should be specified in the narrative section of the SAE report form.

* + 1. Follow-up

Described elsewhere.

* 1. Reporting

**Documentation and Reporting of AEs**

Any AE defined in clinical study protocol as relevant for the evaluation and analysis of the clinical trial has to be documented in the CRF on the respective Adverse Event Report Form. Documentation and evaluation of each AE occurring between:

the visit with the first administration of IMP to the subject and

up to 30 days after the subject has received the last dose of trial drug

According to the CTR, only adverse events and unexpected clinical diagnostic findings that are identified in the protocol as critical to safety evaluations must be reported by the investigator to the sponsor.

All medical conditions prevalent prior to study enrolment and all Adverse Events (AE) that occur after first dosing and within 30 days of discontinuation of dosing will be collected throughout the study and documented in the subject’s medical record using medical terminology and transferred to the CRF. If applicable, AEs and SAEs that relate to any later protocol-specified procedure will be recorded. Furthermore, the should report any SAE that occurs after these time periods and after end of study, if the SAE is believed to be related to the study drug. An SAE report should be completed for any event where doubt exists regarding its seriousness. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology. All measures required for adverse event management must be recorded in the source document and reported according to sponsor`s instructions. The investigator evaluates all Adverse Events regarding severity, causality as well as seriousness.

This includes laboratory deviations that meet the following criteria:

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).

(S)AEs should be followed to resolution or stabilization. Non-serious AEs should be reported as SAEs if they become serious.

**Documentation and Reporting of SAEs**

Every SAE has to be reported immediately to the sponsor except those SAEs the protocol identifies as not requiring immediate reporting.

The documentation of the SAEs for a patient is carried out as described under 12.4, the reporting of SAEs for study patients is carried out within the following time periods:

after the subject has been randomized and has received trial drug for the first time (Baseline, Visit 1)

up to 30 days after the subject has received the last dose of trial drug

after these time periods until end of study, when the SAE is believed to be related to the study drug

after the end of trial when the investigator becomes aware of a SAE with a suspected causal relationship to the IMP

Any SAE occurred after application of study drug should be reported immediately after investigator awareness of the event to the sponsor (at the latest within 24 hours):

Study Coordinating Center of the SZB /Studienzentrale Studienzentrum Bonn (SZB)

FAX: +49 (0)228 287 9080110

E-Mail: [safety-szb@ukbonn.de](mailto:safety-szb@ukbonn.de)

Reporting should occur by fax on the SAE report form provided for this purpose. Symptoms, signs and laboratory changes should, as far as possible, be combined into one single diagnosis. The investigator is responsible for assessing the event (seriousness, intensity, causality). If necessary information is not fully available at this time, follow-up reports should be sent as soon as possible. Questions must be answered promptly. Further information and details how to report are described in the Safety Management Plan.

* + 1. Regulatory Reporting Requirements

**AEs**

The sponsor shall submit the documentation of AEs to the responsible national competent authority upon request.

**SUSARs**

Regarding suspected unexpected serious adverse reactions (SUSARs) the sponsor has to inform the national competent authority and if applicable the responsible ethics committee and the investigators participating in the clinical trial. The sponsor shall report electronically and without delay to the European Medicines Agency (EMA) via database Eudravigilance all relevant information about SUSARs to IMPs occurring in that clinical trial or occurring in any of the subjects of the clinical trial, which are identified by or come to the attention of the sponsor after the end of the clinical trial.

The period for the reporting of SUSARs by the sponsor shall take account of the seriousness of the reaction:

* in the case of fatal or life-threatening SUSARs, as soon as possible and in any event not later than seven calendar days after the sponsor became aware of the reaction, followed by as complete a report as possible within 8 additional calendar days;
* in the case of non-fatal or non-life-threatening SUSARs, not later than 15 calendar days after the sponsor became aware of the reaction.

**Re-examination of the risk-benefit assessment**

The sponsor shall rapidly inform the national competent authority(ies) (NCA) of any information that might materially influence the benefit-risk assessment of a medicinal product or that would be sufficient to consider changes in medicinal product administration or in the overall conduct of a clinical investigation represents such situations. This includes in particular:

* For an "expected," serious ADR, an increase in the rate of occurrence which is judged to be clinically important.
* A significant hazard to the patient population, such as lack of efficacy with a medicinal product used in treating life-threatening disease.
* A major safety finding from a newly completed animal study (such as carcinogenicity).

**Annual Safety Report (ASR)**

The sponsor provides an annual report on the safety of the trial participants to the responsible ethics committee and the national competent authority at least once a year during the clinical trial or upon request. The safety report is prepared in accordance with article 43 CTR.

The data-lock point of the patient data included and analyzed in the report refers to the date of approval of the clinical trial by the national competent authority. The sponsor will provide the report within 60 days of the datalock point annually.

**Arrangements to protect trial participants against imminent danger**

Whenever the safety of subjects is compromised and the sponsor and investigator are taking measures to protect subjects from imminent danger, the sponsor has to inform the responsible ethics committee and the national competent authority of such arrangements and their underlying circumstances, as soon as possible.

* + 1. Adverse Events of Special Interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor’s product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. AESIs are defined on the basis of an ongoing review of the safety data.

* + 1. Disease-related Events or Outcomes Not Qualifying as AEs or SAEs

**Serious Adverse Events Exempted from Expedited Reporting**

In this clinical trial no exemptions defined.

* + 1. Adverse Event Reporting for Specific Situations

**Potential Drug Induced Liver Injury (DILI)**

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

NOTE: Although potential drug-induced liver injury (DILI) is not always serious by regulatory definition, these events must be reported within the SAEs timeline as medical important event, if no other SAE criteria is applicable.

Potential drug induced liver injury is defined as:

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

AND

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

AND

1. 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.

**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.

Product quality complaints see 9.4.5.

* + 1. Product Quality Complaints (PQCs)
       1. 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.

* + - 1. Reporting

Product Quality Complaints must be reported by investigator or pharmacy to **BMS within one (1) business day** of awareness to [**IMPQualityComplaints@bms.com**](mailto: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.

* + 1. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (which are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment), should be recorded on the adverse events eCRF page. Whenever possible, a diagnosis, rather than a symptom, should be provided. Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the lab/test result as an additional event.

See also 12.4 and 12.5.1

* 1. Pregnancy and Postpartum Information
     1. Participants Who Become Pregnant During the Trial

Women of childbearing potential are required to have a negative urine/serum β-hCG pregnancy test to exclude a pregnancy before being enrolled in the clinical trial. Furthermore, females of childbearing potential have to use medically reliable methods of contraception for the entire study duration.

Any pregnancy that occurs during study participation must be reported to the Sponsor. To ensure subject safety, each pregnancy must be reported to the Sponsor Delegated Person/Coordinating Investigator and the SZB. For this purpose, the investigator documents and reports the pregnancy on the registration form provided for this purpose and remits this immediately (at the latest after 24 hours) to the Sponsor Delegated Person/Coordinating Investigator and the SZB.

**Study Coordinating Center of the SZB /Studienzentrale Studienzentrum Bonn (SZB)**

**FAX: +49 (0)228 287 9080110**

**E-Mail:** [**safety-szb@ukbonn.de**](mailto:safety-szb@ukbonn.de)

The pregnant subject has to discontinue the treatment with the IMP permanently and has to be excluded from the trial.

The pregnancy itself is not classified as an AE or an SAE, but must be followed up to determine outcome (including premature termination) and status of mother and child. According to CTR (Annex III 2.1), pregnancies shall be subject to the same obligation to report as adverse reactions. The investigator will request this information after the scheduled date of birth and provide it in writing to the (sponsor/sponsor's representative).

Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the investigator’s attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be reported.

In addition to this information, the investigator will also ask about the planned date of birth and inform the (sponsor/representative of the sponsor) in writing.

If the outcome of the pregnancy corresponds to one of the following cases

* spontaneous or therapeutic abortion or voluntary abortion
* stillbirth
* the presence of birth defects, or
* congenital anomalies (also in miscarriages, stillbirths or premature death) the investigator reports this case as SAE. In the case of stillbirth, the (presumed) causality is documented.
  + 1. Participants Whose Partners Become Pregnant

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 sponsors registration form provided for this purpose. 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.

1. Statistical Considerations
   1. General Considerations

Full details of all statistical analyses will be specified in a separate Statistical Analysis Plan (SAP), which will be finalized prior to locking and unblinding of the study database. A summary of the proposed methods of analysis is provided below.

This is a prospective, phase II, national, multicenter, randomized, double-blind, 2 arm parallel, placebo-controlled clinical trial. The efficacy assessment phase of the trial (16 weeks) will be followed by an optional open-label extension phase (32 weeks). See also Section 8

* + 1. Two-stage Reporting

A primary analysis is planned after the last patient has completed the double-blinded trial phase at visit 4. The primary analysis and interim report will describe subject recruitment, treatment compliance, the safety and tolerability for the subjects in this phase. Furthermore, it will include the analyses of efficacy of deucravacitinib on objective clinical symptoms/ disease activity (LiPADI Activity Score; primary objective and endpoint) as well as its effect on quality of Life (DLQI), itching (NRS) and usage of steroids, all until day 112. An updated final report including the analyses of all endpoints and objectives will be generated after end of the open label extension phase

* 1. Analysis Sets

This is proof-of-concept trial with the aim to evaluate the efficacy of deucravacitinib in the target population. Therefore, the main analysis population (Full Analysis Set - FAS) will comprise patients with a minimum of compliance level (for details see Ch. 10.8), but otherwise irrespective of the occurrence of any intercurrent events (e.g. whether other protocol violations are revealed).

The per-protocol (PP) population is a subset of the FAS population and is defined as the group of subjects who had no major protocol violations, received a predefined minimum dose of the treatment and underwent the examinations required for the assessment of the endpoints at relevant, predefined times i.e. representing a hypothetical population without intercurrent events and adhering to the protocol. The analysis of the PP group will be performed for the purpose of a sensitivity analysis.

Additional sensitivity analysis will be performed on a completer set, which is a subset of the FAS population having an assessment at Week 16

* 1. Analyses of Demographics and Other Baseline Variables

See SAP.

* 1. Analyses Associated with the Primary Objective(s)
     1. Statistical Method of Analysis

Statistical analysis will be performed at the Institute of Medical Biometry, Informatics and Epidemiology (IMBIE) at the University of Bonn Medical Center.

All (primary and secondary) endpoints will be summarized using frequency tables and descriptive statistics. These summaries will be provided both for original assessments and for the changes from baseline (if applicable) by treatment and time of assessment. Differences between treatment groups will be estimated according to the character of the variables (categorical or continuous) together with the corresponding 95% confidence intervals.

Proportions will be compared (in a purely descriptive manner) using Fisher’s exact test (stratified by the parameters applied for the treatment assignment) and by means of logistic regressions accounting for the effect of treatment and of the stratification factors. In case of a relevant unbalance between the treatment groups at baseline additional analysis may be envisaged using a logistic regression model accounting also for the relevant baseline variables.

Continuous endpoints will be compared by means of an ANOVA Model (or corresponding non-parametrics test) accounting for the effect of treatment and of the stratification factors. In case of unbalance at baseline additional ANOVA model accounting for the relevant baseline variables as covariates will be used to calculate the corresponding estimates

* + 1. Handling of Data in Relation to Primary Estimand(s)

The primary endpoint of the trial is the change from baseline (Visit1, week 1) to EOS (Visit 4, week 16) of the Lichen Planus Activity and Damage Index (LiPADI) Activity Score.

* + 1. Handling of Missing Data
* Subjects dropping out of the trial prior to randomization will be listed including the reason of drop-out.
* Subjects dropping out of the trial after randomization will be analysed using all available data.

Missing values for the analysis of the endpoints will be treated as such. An additional sensitivity analysis will be performed by applying likelihood based methods (like logistic regression or mixed linear models) to explore the influence of missing observations.

Subjects with insufficient compliance (see chapter 10.8) will be withdrawn from the trial and replaced.

More details will be given in the statistical analysis plan. A check of a possible treatment effect on the frequency of missing values will be done.

* + 1. Supplementary Analysis
       1. Gene Expression Analyses

Expression profiles before and after treatment will be compared in the different treatment arms. An IFN-Signature Score will be collected (gene-expression count of CLE-typical selected IFN-associated genes (e.g. CXCL10, CXCL9, CCL5, MxA, BLyS, TRAIL etc). Further parameters may be included at the discretion of the investigator.

* 1. Analysis Associated with the Secondary Objective(s)
     1. Statistical Method of Analysis

See above

* + 1. Handling of Data in Relation to Secondary Estimand(s)

• Change in the LiPADI Activity Score from baseline (V1) to V3, V4/OLE-V1, SC-1, SC-2, OLE-V2, SC-3 and OLE-V3 in both arms

• Differences in IFN gene expression profile (CXCL10, CXCL9, CCL5, MxA, BLyS, TRAIL etc.) in peripheral blood and skin (BOS/V1, EOS/V4, OLE-V3) between placebo- and treatment-arm

• Change in IFN gene expression profile (CXCL10, CXCL9, CCL5, MxA, BLyS, TRAIL etc.) in peripheral blood and skin (BOS/V1 vs EOS/V4 vs OLE-V3) in both arms

• Change of DLQI from baseline (V1) to EOS (V4) between placebo- and treatment-arm

• Change of DLQI from baseline (V1) to V3, V4/OLE-V1, SC-1, SC-2, OLE-V2, SC-3, OLE-V3 in both arms

• Change of Itch NRS from baseline (V1) to EOS (V4) between placebo- and treatment-arm

• Change of Itch NRS from baseline (V1) to V3, V4/OLE-V1, SC-1, SC-2, OLE-V2, SC-3, OLE-V3 in both arms

• Change in the amount of steroids used from baseline (V1) to EOS (V5) between placebo- and treatment-arm

* 1. Analysis Associated with the Exploratory Objective(s)

Not applicable.

* 1. Safety Analyses

See above.

* 1. Other Analyses

Not applicable.

* 1. Interim Analyses
     1. Interim Report

Based on the interim analysis by the responsible biostatistician after completion of the double-blinded phase (visit 4) of all patients, an integrated medical and statistical interim report will be prepared and signed jointly with the biostatistician. The interim report will describe subject recruitment, treatment compliance, the safety and tolerability for the subjects in during the double-blinded phase. Furthermore, it will include the analyses of efficacy of deucravacitinib on objective clinical symptoms/ disease activity (LiPADI Activity Score; primary objective and endpoint) as well as its effect on quality of Life (DLQI), itching (NRS) and usage of steroids, all until day 112.

The interim trial report will be written and signed by the Sponsor Delegated Person.

* 1. Multiplicity Adjustments

Not applicable.

* 1. Sample Size Determination

This is a proof of concept trial aiming to generate primary data on the safety and efficacy of oral deucravacitinib in lichen planus patients. Therefore, the primary goal is more to estimate the effect size rather to perform confirmatory testing. Consequently, the designated number of subjects to be included in the trial are not calculated based on statistical reasoning but is mainly determined by practical reasons.

The primary endpoint of the trial (the change in the activity part of LiPADI score) with group sample sizes of 10 and 20 patients produce a two-sided 95% confidence interval with a distance from the difference in means to the limits that is equal to approximately 4 score points when the estimated standard deviation is 5 in both groups. Simultaneously, with a standard deviation of 5 score points, the intended two-sided t-test with a type I error rate of 5% will have the power of approximately 80% to detect a difference of 5.7 score-point between treatment groups, which is of clinical relevance (see Stepien et al.2022).

The NRS for itch the can be used to assess the feasibility of the envisaged sample size of 10 subjects in the placebo and 20 subjects in the verum group.

Based on own experience and published data (Phan et al., 2012) we expect a standard deviation of about 1.8 points for the change from baseline of the NRS for itch. Assuming this standard deviation, the intended two-sided t-test with a type I error rate of 5% will have the power of approximately 80% to detect a difference of 2.0 score-point between treatment groups.

The sample size of 10 and 20 subjects and a standard deviation of 1.8 in both groups would simultaneously result a precision of the estimate of the mean differences (as characterized by the half-width of the 95% confidence interval) less than 1.43.

1. Trial Oversight and Other General Considerations
   1. Regulatory and Ethical Considerations

The trial will be conducted in compliance with the protocol, the Regulation (EU) No 536/2014, Regulation (EU) 2016/679 (GDPR) and with the principles of good clinical practice (GCP

**Audits and Inspections**

In accordance with ICH GCP this trial may be selected for audit by representatives of the sponsor, for inspection by site responsible representatives of the local regulatory authority or national competent authority. The investigator and institution involved in the clinical trial permit clinical trial-related monitoring, audits and regulatory inspections, including provision of direct access to source data and documents and agree to support the sponsor to solve possible audit or inspection findings concerning the trial conduct at the respective site.

After every audit the auditee(s) will receive an audit confirmation by the auditor. This document has to be filed together with the trial documentation and has to be made available also to the authorities in case of an inspection.

At the end of the trial, a copy of the audit certificate(s) will be included in the final report.

**Ethics Committee and Competent Authority(ies)**

The clinical trial protocol and amendments have to be approved by the National Competent Authorities (NCA), in addition to protocol and amendments the subject information and informed consent, and any other written information to be provided to the trial subjects have to be approved by the responsible ethics committee (“zuständige Ethikkommision”).

The sponsor delegated person will authorize the Study Coordinating Center of the SZB with submitting the documents to the Ethics Committee(s) (EC) and to the NCA via the EU portal Clinical Trials Information System (CTIS).

A copy of the written approval must be received by the sponsor delegated person before recruitment of subjects into the trial and shipment of trial drug.

Any substantial amendments to the protocol or subsequent changes to the informed consent form as a result of changes to the protocol must also be submitted to the EC/NCA via CTIS. Records of the regulatory review, communication and opinion of all documents pertaining to this trial must be kept on file by the investigator and are subject to regulatory authority and / or sponsor inspection during or after completion of the trial.

The sponsor/sponsor delegated person/ Study Coordinating Center of the SZB will provide a safety update of the trial to the EC(s)/NCA, including line listing, individual reports of SUSARs, if applicable, annually or more frequently if requested. Furthermore, SZB will perform applicable notifications in CTIS such as start of recruitment, start of trial.

At the end of the trial, the sponsor/sponsor delegated person/Study Coordinating Center of the SZB will notify the EC(s)/NCA via CTIS about the trial completion. A copy of all reports submitted to the EC will be sent to the sponsor

* 1. Trial Oversight
     1. Investigator Responsibilities

By signing this protocol the local investigator declares his/her commitment:

* to not enrol any person dependent on him/her or the sponsor in accordance with the principles of ICH-GCP
* to follow the applicable regulations for data privacy and security according to CTR and GDPR
* to inform the subjects of the transmission of their pseudonymized data according to documentation and transmission obligations (CTR Article 56) and to make sure that subjects unwilling to give consent to the processing of their data are not included into the trial
* to certify that he/she is familiar with the appropriate use of the IMP, as described in this protocol, the current Investigator´s Brochure and Summary of Product Information, if applicable
* to be qualified by education, training and experience to assume responsibility for the proper conduct of the subject
* to be thoroughly familiar with the appropriate use of the trial drug(s), as described in the protocol, the product information and other information sources provided by the sponsor
* to be aware of, and comply with GCP and the applicable regulatory requirements
* to maintain a list of appropriately qualified persons to whom the investigator has delegated significant subject related duties (if applicable)
  + 1. Sponsor Responsibilities

According to CTR and German Medicinal Products Act (AMG §§ 40 – 42) the sponsor is responsible for obtaining approval from the national competent authority and the responsible ethics committee before initiation of the trial.

During the clinical trial, quality control and quality assurance will be endured through monitoring, auditing and inspections by authorities.

**Quality Management**

During the clinical trial, quality control and quality assurance will be endured through monitoring, auditing and inspections by authorities.

**Risk Assessment**

In line with ICH-GCP 5.0 the sponsor implements a quality management system using a risk-based approach that entails the identification of critical processes/ data and associated risks. The risk identification, evaluation, control, communication and review is performed according to standard operating procedures.

**Monitoring**

To ensure accurate, complete, consistent, and reliable data, the investigator’s site(s) and trial procedures will be monitored by a representative of the sponsor. The sponsor’s representative will visit the site: • to evaluate the progress and recruitment of the trial, • to review the source documents and CRFs for protocol compliance, accuracy and validation, • to assess facilities and equipment, • to check for protocol compliance, • to assure the AE/SAE reporting, • to verify proper handling and dispensing of the IMP(s), and other factors. Frequency and scope of the monitoring visits will be defined in the Monitoring Plan for this trial which also includes the extent of source data verification that is required. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and resolved, and therefore ensures the accuracy and consistency of the trial with GCP and all applicable laws. The investigator allows the monitor to have access to all trial related original data and documents relevant for the monitoring of the trial>

* 1. Informed Consent Process

If a subject appears to be eligible for the trial, the investigator will inform the subject about the trial and ask the subject for his/her written consent.

It is a requirement that written consent is obtained prior to any trial-specific procedures. The investigator will then record the details of the eligible subjects on trial specific lists provided.

* + 1. Subject Identification

• The participants are identified on the basis of internal clinic data of already known patients that reveal them as potential study participants. They may be subsequently contacted in writing or by telephone. In addition, subjects are also identified by personal presentation in the outpatient clinic (either by new presentation or by re-presentation in the case of regular presentation to the university outpatient clinics).

Furthermore, the study will be accessible to interested subjects via the “Study Register” on the SZB homepage.

* + 1. Recruitment Resources

• Subjects who are already known in the clinic or who present themselves for the first time in the department and appear to be eligible for the study are informed immediately while still on site, by post or telephone. In a detailed discussion with the doctor (either regularly at the presentation in the outpatient clinic or at screening), the study including rationale and procedure is explained to the subject. In addition, the subject receives information material in the form of a consent form for participation in the study, in which the study is also described in detail. The subject is offered to contact the trial site at any time if it has any concerns or questions in this context.

* + 1. Informed Consent Procedure

According to Art. 29 CTR and § 40b of the German Medicinal Products Act (“Arzneimittelgesetz (AMG)”) every participating clinical trial subject will be informed of nature, objectives, benefits, implications, importance, treatment methods, risks, consequences and inconveniences of the trial by the local investigator. Details of indemnity and insurance are also stated.

The local investigator is responsible for obtaining written informed consent from a subject before any protocolspecific screening procedures will be performed or any investigational products will be administered. The written informed consent document has to be prepared and provided in the language(s) of the potential subject population.

It is also the responsibility of the investigator for asking the subject if he/she agrees to have her the primary care physician informed of his/her participation in the clinical trial. If the subject agrees to such notification, the investigator shall inform the primary care physician of the subject’s participation by sending a message letter.

Subjects must understand that it is their own free will to participate and that they can withdraw consent at any time without giving reasons and without penalty or loss of benefits to which the subject is entitled. Also, subjects must understand that they will experience no disadvantage as a result of this decision and that no alternative therapy will be withheld by the investigator.

The subject will be given ample of time and opportunity to obtain answers to any open questions. All questions relating to the clinical trial should be answered to the satisfaction of the subject. On the other hand by personally signing the consent form subjects give their consent to the evaluation, recording and usage of their personal data according to § 40b Abs. 6 AMG.

The written consent form will be personally dated and signed by the subject and the by investigator conducting the informed consent discussion. The informed consent forms will be filed in the Trial Site File (ISF) at each site.

The acquisition of informed consent and the subject’s agreement or refusal of the notification of the primary care physician should be documented in the subject’s medical record.

A copy of the signed and dated informed consent form will be given to the subject and a copy will be held in the subject’s medical notes. The existence of written informed consent will have to be confirmed before any trial-specific test/treatment has been performed.

In the case of substantial amendments, e.g. any new data providing information on the safety profile of any of the investigational medicinal product and leading to significant changes in the risk-benefit ratio, the subject must be informed with an appropriately revised subject information and the consent of the subject has to be obtained again.

Changed trial procedures can only be carried out if they have been approved authorized by the national competent authority and the leading responsible Ethics Committee, and if the subject has been appropriately informed and has given his/her written consent.

* 1. Committees

**Data Safety Monitoring Board (DSMB)**

In this trial there is no Data Safety Monitoring Board (DSMB) involved. >

* 1. Insurance and Indemnity

Every subject participating in the trial is insured against any trial-related illness/injuries pursuant to the legal requirements which may occur during the trial, in Germany according to § 40 Nr.3 AMG.

Excluded from this, however, are injuries to health and deterioration of illnesses already in existence which would have continued to exist even if the subject had not taken part in the clinical trial.

The investigator will inform the subject of the existence of the insurance, including the obligations arising from it. The subject must be afford access to insurance documents and provided with a copy of the general conditions of insurance on request.

The insurance cover is jeopardized if the subject fails to immediately report to the investigator or responsible physician any injury to health which might have resulted from the participation in the clinical trial, or if she/he undergoes any other medical treatment (except for emergency treatment) without the investigator’s knowledge before her/his participation in the clinical trial has officially ended.

In case of any health impairment the subject is obliged to notify the insurance and additionally the investigator as soon as possible. The investigator is obliged to make a report to the sponsor.

The subject insurance will be arranged by sponsor/sponsor delegated person. The insurer will be:

Name of Insurer: HDI Global SE

Insurance Number: 57 010323 03010/03604

Address: HDI-Platz 1, 30659 Hannover

Insurance Broker: Ecclesia Universitätskliniken Ecclesiastraße 1 - 4, D-32758 Detmold

Phone: +49 (0)5231 / 603-0

Fax: +49 (0)5231 / 603-603-197

E-Mail: [info@ecclesia-unikliniken.de](mailto:info@ecclesia-unikliniken.de)

This insurance covers trial related injuries to health up to a maximum of 500.000 Euro per subject and 50 Mio. Euro for the entire study.

* 1. Risk Management
     1. Compliance with the Protocol

The investigator should conduct the clinical trial in compliance with this protocol. For this purpose, the document will be signed by the sponsor and the investigator. As a general rule, the investigator should not deviate from the protocol or make amendments to the protocol without the agreement of the sponsor/authority/ethics committee (unless subject safety is at risk, see below).

Any deviations from the approved protocol should be documented and explained by the investigator or an individual who is designated by the investigator.

The investigator may deviate from the protocol or make an amendment to the protocol without prior approval of the ethics committee to eliminate immediate risks to the subjects. The deviation or amendment should subsequently be reported to the ethics committee, the sponsor or sponsor delegated person and, if necessary, the competent authority, giving reasons.

In case of general or local restrictions due to an altered COVID-19 situation, the investigator may deviate from the protocol to follow recommendations of the Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic (Version 5, 10/02/2022). The deviation or amendment should subsequently be reported to the ethics committee, the project leaders, giving reasons.

* + 1. Serious Breach

Protocol violations that constitute a serious breach according to Art. 52 CTR will be reported to the national competent authority(ies) and responsible ethics committee no later than 7 days after becoming aware of that breach.

Deviations from this clinical study protocol or CTR may constitute a serious breach if they are likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial (Art. 52 CTR). The sponsor shall notify the Member States concerned about a serious breach at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.

Default definition and management of protocol violations are described in a Standard Operation Procedure of the SZB The following deviations should in any case be considered a serious breach:

* fraud
* documented informed consent not available
* clinical trial conduct without available regulatory authorization
* systematic or significant mis-dosing
* lack of SUSAR reporting, results in trial participants being put at a significant degree of risk
* deviations that lead to removal of data from the trial analysis
* severe violation of data privacy rules

Protocol violations will be reported to the sponsor/sponsor delegated person during the course of the trial in the monitoring reports and to the sponsor to:

E-Mail: [**Serious-breaches@ukbonn.de**](mailto:Serious-breaches@ukbonn.de)

Telephone: **+49 (0) 228-287 16849**

* + 1. Notification of General Amendments to the Protocol

The sponsor can make general amendments to the protocol after the clinical trial has started. These may be of an administrative nature (logistical/administrative amendments) or substantial.

Substantial Amendments are changes that likely affect and /or change:

* the safety of the persons concerned,
* the interpretation of the scientific trial documents or the scientific informational value of the trial results,
* the nature of management or conduct of the clinical trial (e.g. change of coordinating investigator (formerly German LKP), sponsor or sponsor's deputy),
* the pharmaceutical quality or safety of the investigational medicinal products
* the risk assessments concerning the health of persons who are not concerned, or the environment, in clinical trial with drugs consisting of or containing genetically modified organisms

require an new authorization of the NCA and a new favourable opinion by the Ethics Committee.

The clinical trial may only be continued after authorization for the substantial modification has been obtained from the competent ethics committee and the NCA.

If applicable, an updated Informed Consent Form has to be signed by all subjects enrolled in the trial who are affected by the amendment.

If administrative protocol changes (e.g. change of monitoring, telephone numbers) are necessary, the EC and NCA will be notified via CTIS only.

* + 1. Notification of the End of the Trial

The end of the clinical trial is the date of the last visit of the last subject undergoing the trial.

According to Art. 37 CTR, the ECs and NCAs of all member states concerned will be notified via CTIS about the end of the clinical trial.

Within one year of the end of the complete trial a summary of the trial report will be provided to the NCA(s) and EC(s) via CTIS. This includes a summary that is understandable to laypersons and which fulfills the requirements of Annex V CTR.

* 1. Data Governance
     1. Data Protection and Subject Confidentiality

The pertinent provisions of the country-specific legislation on data protection must be fully complied with.

The collection, transmission, archiving and evaluation of personal data in this clinical trial are performed according to local applicable laws (Data Protection Act, General Data Protection Regulation). Prior to trial participation each subject must be informed by the investigator about the purpose and extent of the collection and use of personal data, particularly medical data and must give written informed consent.

The subjects must be informed that:

1. Any subject related data in this trial are handled confidentially and will be captured in pseudonymized form (subject ID number for the trial – subject number-, year of birth) and will only be transmitted to
   1. the coordinating investigator/sponsor/sponsor delegated person/data monitoring safety board for scientific and adverse event evaluation
   2. the national competent authority(ies) (in Germany: BfArM or PEI), the responsible EC and the European Clinical Trial Information System (CTIS) for verifying the proper conduct of the trial and for assessment of trial results and adverse events
2. During monitoring, audits or inspections representatives of the sponsor (monitor, auditor) or of the local regulatory authority(ies) must have direct access to personal data. In this case, the investigator is released from confidential medical communication.
3. Consent to the collection and processing of personal data within the scope of this clinical trial can be revoked at any time. A subject is informed that he/she can terminate his/her participation in the clinical trial at any time - without giving reasons and without any of the following disadvantages. In the event of revocation of the declaration of consent, the data stored up to this point in time will continue to be used without mentioning names, insofar as this is necessary to determine the effects of the medicinal product under investigation and to ensure that the interests of the person concerned which are worthy of protection are not impaired, or to comply with the obligation to submit complete approval documents.
   * 1. Data Security Breach

Data security breaches are handled as serious breaches. Please refer to section 18.5.

* + 1. Data Sharing Statement

Individual participant data will be available (including data dictionaries).

Individual participant data (including data dictionaries) that under-lie results concerning primary or secondary endpoints reported in a published scientific article will be shared on demand after de-identification. Furthermore, the following documents will be made available at leased: Study Protocol and Informed Consent Form.

The data will be beginning 6 months and ending 3 years following article publication.

Data are made available to researchers after a methodologically sound scientific proposal has been submitted to the Coordinating Investigator a steering committee consisting of the Coordination Investigator, the representative of the Coordinating Investigator, and a SZB member has approved the proposal, and a data access agreement has been signed. Study protocol and the informed consent forms will be made available on demand. After 36 months the data will be available in our University’s data warehouse but without investigator support other than deposited metadata.

* 1. Source Data
     1. Data Management

The Clinical Study Core Unit, Study Center Bonn will carry out data management of the study.

The study data is recorded and stored in a suitable, validated CDMS (Clinical Data Management System). Details on data management (procedures, responsibilities, data corrections, if any, which may be made by Data Management staff themselves, etc.) will be described in a data management plan prior to the trial. During the trial, the performance of data management and any deviations from the data management plan will be documented in a data management report. Queries and edit checks will be specified in a data validation plan. Before any data entry is performed, the trial database will be validated and the technical specifications of the database will be documented in a variable-plan.

The study data is entered into the study database directly at the center by trained staff. The access and processing rights in the study database are defined by predetermined roles. An audit trail is kept to track changes. Queries are generated by the CDMS itself, displayed to the testing personnel and answered in the system. The data management personnel systematically monitor the correctness and completeness of the data input. For more complex queries or checks, external CDMS programs created with the SAS soft-ware can be used.

* + 1. Data Coding

The following clinical data are to be recorded using a standardized coding system:

* The description of AEs with MedDRA

The versions of the coding systems to be used are defined in the Data Management Plan.

* + 1. Documentation of Trial Data
       1. Documentation of Trial Data in the Medical Record

The investigator will record the participation in the trial, the frequency of the trial visits, the relevant medical data, the concomitant treatment and the occurrence of adverse events in the medical record of each subject.

Data collected on the CRFs must match the sources data. These may include but are not limited to the hospitals’ or the physician's medical files, laboratory and pharmacy records, diaries etc. A source data location list will be filed in the ISF.

In some cases, the CRF, or part of the CRF, may also serve as source document. In these cases, a document should be available at the investigator’s site that clearly identifies those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

* + - 1. Case Report Form (CRF)

The investigator has ultimate responsibility for the accuracy, authenticity, timely collection and reporting of all clinical, safety, laboratory data entered on the CRFs. All these data may only be entered into the CRF by authorized trial personnel as promptly as possible.

An Electronic Data Capture (EDC) System will be used in this trial (eCRF called hereinafter) using the Software MARVIN XClinical. All data collected during the trial will be documented electronically on the trial-specific CRF pages by the responsible investigator, or an individual who is designated by the investigator, as timely as possible. Entry and corrections on e-CRF pages are automatically documented via “audit trail” created by the program. The investigator signs completed data electronically.

The monitor is responsible to verify the eCRF at regular intervals throughout the trial to verify the adherence to the protocol, completeness, accuracy, and consistency of the data. Therefore the monitor should have access to subject medical records and other trial-related records needed to verify the entries on the eCRF.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits, including delays in completing eCRF are resolved.

A clinical data management review will be performed on subject data entered in the eCRF database.

A separate eCRF-Manual is available to support the data entry.

Further, the questionnaires LiPADI Activity Score, Itch-NRS and DLQI will be used. For details see 11.1.9.

* + 1. Source Data Verification (SDV)

Source data verification will be performed in order to verify the accuracy and completeness of the entries on the case report form (CRF) by comparing them with the source data, and to ensure and increase the quality of the data. All data which are subject to SDV must have been entered in the medical record or, in the case of source documents, enclosed with the medical record. The investigators will afford the CRA access to the medical records for the performance of SDV.

Source data as defined by ICH-GCP include data such as hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. Source data and corresponding source documents should be documented for each clinical trial site on a Source Data Location List.

The extent of SDV will follow a risk-based approach and will be laid down in the Monitoring Plan

* + 1. Investigator Site File

The trial site will be provided with a Clinical Trial Master File (investigator site file (ISF)) containing all sponsor-specific essential and trial specific documents. The monitor will regularly check the ISF for accuracy and completeness. The trial site file has to be stored locked and sure. After end of trial or early termination of the trial the ISF should be retained for 25 years at the site.

The ISF includes the subject identification list, where the investigator has to record the trial participation of each subject. This list allows identification of each subject and contains the subject number, the name, telephone number (if applicable), birth date and the date of inclusion of the subject into the trial, and will be reviewed by the monitor for completeness. After end of the trial the subject identification list remains with the subject site, no copies will be provided to the sponsor nor monitor. In addition, trial participation of the subject should be recorded in the subject chart (trial drug, screening/randomization number, start and end date of the trial).

The investigator will maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. This list will be filed with the ISF, too.

Furthermore, trial personnel responsible for documentation in the CRFs should be identifiable. Therefore, a signature list with the name, signature, initials/abbreviation and trial responsibilities of all persons who are allowed to make entries into the CRF will be filed in the ISF.

Trial documents provided by the sponsor/ Study Coordinating Center of the SZB are confidential and may not be made accessible to third parties not involved in the trial by the investigator or other staff members. All trial data are collected pseudonymously.

* + 1. Archiving
       1. Sponsor

The sponsor must retain all essential documents inclusively the case report forms (Subject Master File) for the duration of at least 25 years after end or stop of trial. The sponsor must archive all trial related documents according to regulatory requirements.

* + - 1. Investigator

The investigator should maintain all subject documents as specified in Essential Documents for conduct of a clinical trial (see ICH-GCP, section 8) and as required by the applicable regulatory requirement(s) after completion of the clinical trial so that they will be available for audits and inspections by the authorities. The investigator will be responsible for the storage.

The following retention periods will apply after completion or stop of the clinical trial:

* all essential documents and trial related data must be retained securely for at least 25 years (CTR Art. 58),
* medical records of subjects and other source documents shall be archived in accordance with national law.

The investigator/institution should take arrangements to prevent accidental or premature destruction and illegitimate access to these documents.

To enable evaluations and/or audits from regulatory authorities or the sponsor, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e. g. CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, drug accountability and adequate documentation of relevant correspondence (e. g. letters, meeting minutes, telephone calls reports).

The trial site will maintain a file of essential subject documentation (Trial site File). It is the responsibility of the site to retain copies of all completed CRFs for the subject and their trial file on site.

* + - 1. Destruction of Study Documents

Study documents may not be destroyed by study site personnel prior to the retention period specified above without the prior written consent of the sponsor. The principal investigator must inform the sponsor in due time if the principal investigator leaves the institution during the retention period. This rule also applies when the institution closes within the retention period.

* 1. Protocol Deviations

Protocol violations are major deviations from the procedures outlined in this document like:

* missed evaluations
* incorrect timing of evaluations
* relevant non-compliance with investigational medicinal product, if applicable
* the intake of medications not allowed
* any non-adherence to the protocol that would have an impact to the subject’s rights, safety or welfare and or reliability and robustness of study data

After a subject has been enrolled, it is the investigator’s responsibility to make a reasonable effort to correct any protocol violations and to continue the subject’s participation in the trial, if possible.

Protocol violations do not constitute a justification for withdrawal of a subject from the trial themselves.

Protocol violations will be reported to the sponsor/sponsor delegated person during the course of the trial in the monitoring reports.

All protocol violations will be listed and the impact on the evaluation of the subjects concerned will be discussed prior to statistical analysis

* 1. Early Site Closure

See Section 7 Discontinuation or Withdrawal from the Trial

1. Appendix: Supporting Details
   1. Clinical Laboratory Tests
      1. Time Schedule of Measurements

This study will consist of three phases: screening, treatment, and optional open label extension period. The study schedule (see section 2) shows the summary of visits and procedures that will take place during the study.

* + - 1. Screening Period

Visit 0 (Day -28 to day -7) – Screening

All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the trial.

Subjects who do not qualify for the study between signing the informed consent and finalizing Visit 0 will be considered screening failures. Subjects who are screening failures during the screening period may be rescreened twice.

All subjects must have the following procedures completed within 28 days (unless otherwise noted) prior to enrollment:

* Review inclusion and exclusion criteria
* Subject information and informed consent
* Demographic data
* Medical history concerning the trial specific illness
* Prior therapies/medications and concomitant medications for treatment of trial specific illness (last 365 days prior to enrollment)
* Medical history (non-trial related illness)/concomitant medications
* Clinical examination
  + Physical examination including height and weight
  + Vital signs: resting systolic and diastolic blood pressure, pulse and temperature
* Laboratory
  + Screening laboratory
  + Pregnancy test (serum) will be performed in all fertile women (women of childbearing potential must have an negative pregnancy test < 7 days prior to first dose)
* Recommendations on contraception methods during participation in the clinical trial will be provided
* Efficacy assessments
  + Lichen Planus Activity and Damage Index (LiPADI) Activity Score
  + Dermatological Quality of Live Index (DLQI)
  + Numeric rating scale (NRS) for average itch during the past 24 hours
  + Photographic documentation of skin condition (only in Bonn)

At the end of the screening period, prior to application of double-blind investigational product, eligible subjects will be randomized (2:1) to one of the two treatment arms (double-blind).

Randomization visit (no subject visit, Day -21 to day -3))

If a patient is eligible to participate in the study according to the in- and exclusion criteria the patient will randomly be assigned to one of the two treatment arms. The randomisation of eligible patients will take place after all screening examinations are completed and prior to the treatment phase. A randomisation code will be assigned for each randomized patient in the eCRF. This code will be used to label all information that is gathered for each patient (e.g. blood samples and electronic case report forms (eCRFs)) and to label the study medication.

* + - 1. Treatment Period

The treatment period will include 4 visits from day 1 until day 112, so the treatment will be extended to a period of 16 weeks.

A delay of ± 3 days is acceptable for all visits (except Baseline/V1 and Safety Follow up).

At the Baseline visit, subjects will be administered the first dose of IMP in the clinic in the presence of study center personnel.

All of the laboratory samples and vital signs will be collected prior to IMP application at the time-points specified in the schedule of activities.

All visits will be performed according to the schedule of activities (see section 2).

Visit 1 (day 1) – Baseline

The following assessments and procedures will be performed at this visit:

* Randomization (if not already occurred in Screening Phase)
* Clinical examination
  + Physical examination
  + Vital signs: resting systolic and diastolic blood pressure, pulse and temperature
  + Check of change of concomitant therapies/ medication since last visit
* Laboratory
  + RLab
  + Lab for mRNA-based gene expression analyses
* Skin sampling: A tape strip is taken from two defined areas of skin (lesional and non-lesional) on each patient
* Efficacy assessments
  + Lichen Planus Activity and Damage Index (LiPADI) Activity Score
  + Dermatological Quality of Live Index (DLQI)
  + Numeric rating scale (NRS) for average itch during the past 24 hours
  + Photographic documentation of skin condition (only in Bonn)
* Occurrence of AEs/SAEs
* Handing out diary
* Drug dispensation (The first intake takes place under supervision, see also 10.8 and 10.10)

Visit 2 (Day 14 ± 3 days) and Visit 3 (Day 56 ± 3 days)

The following assessments and procedures will be performed at this visit:

* Clinical examination
  + Physical examination
  + Vital signs: resting systolic and diastolic blood pressure, pulse and temperature
  + Change of concomitant therapies/ medication since last visit
* Laboratory
  + RLab
* Efficacy assessments
  + Lichen Planus Activity and Damage Index (LiPADI) Activity Score
  + Dermatological Quality of Live Index (DLQI)
  + Numeric rating scale (NRS) for average itch during the past 24 hours
  + Photographic documentation of skin condition (only in Bonn)
* Occurrence of AEs/SAEs
* Drug accountability
* Drug dispensation
  + - 1. End of Study (EOS or premature termination)

Visit 4 is the transition point between the study phase and the open-label extension. For all subjects who decide not to participate in the OLE, the study ends with the visit at V4. For all others, this is the same appointment as the first appointment of the open-label phase.

The end-of-study visit will also take place if a subject has to be excluded early from the study phase or the open-label phase for any reason. Each subject must undergo an end-of-study visit and a safety follow-up visit is mandatory for each subject.

Visit 4 / OLE Visit 1 (day 112 ± 3 days)

The following assessments and procedures will be performed at this visit:

* Clinical examination
  + Physical examination
  + Vital signs: resting systolic and diastolic blood pressure, pulse and temperature
  + Check of change of concomitant therapies/ medication since last visit
* Laboratory
  + RLab
  + Lab for mRNA-based gene expression analyses
* Skin sampling: A tape strip is taken from two defined areas of skin (lesional and non-lesional) on each patient
* Efficacy assessments
  + Lichen Planus Activity and Damage Index (LiPADI) Activity Score.
  + Dermatological Quality of Live Index (DLQI)
  + Numeric rating scale (NRS) for average itch during the past 24 hours
  + Photographic documentation of skin condition (only in Bonn)
* Occurrence of AEs/SAEs
* Drug accountability
* Drug dispensation if applicable (if the subject will continue with open label phase)
  + - 1. Open Label Extension

All subjects who decide to continue will receive an optional 224 days of treatment with deucravacitinib.

This phase will entail 6 visits – 3 full and 3 short visits (short check-ups = SC; OLE-V1, SC-1, SC-2, OLE-V2, SC-3, OLE-V3).

A delay of ± 3 days is acceptable for all visits and short check-ups. OLE-V1 coincidences with Study Visit 4 (EOS) on Day 112.

All tests (incl. a negative pregnancy test result) and procedures of Visit 4/ OLE–V1 have to be completed before the first administration of IMP in the open label extension. The diary must be continued. All subjects will receive deucravacitinib.

All of the laboratory samples and vital signs will be collected prior to IMP application at the time-points specified in the schedule of activities.

OLE–V1 (Day 112 ± 3 days)

The following assessments and procedures will be performed at this visit:

* Clinical examination
  + Physical examination
  + Vital signs: resting systolic and diastolic blood pressure, pulse and temperature
  + Check of change of concomitant therapies/ medication since last visit
* Laboratory
  + RLab
  + Lab for mRNA-based gene expression analyses
* Efficacy assessments
  + Lichen Planus Activity and Damage Index (LiPADI) Activity Score.
  + Dermatological Quality of Live Index (DLQI)
  + Numeric rating scale (NRS) for average itch during the past 24 hours
  + Photographic documentation of skin condition (only in Bonn)
* Occurrence of AEs/SAEs
* Drug accountability
* Drug dispensation if applicable (if the subject will continue with open label phase)

SC-1 (Day 126 ± 3 days), SC-2 (Day 168 ± 3 days) and SC-3 (Day 280 ± 3 days)

The following assessments and procedures will be performed at this visit:

* Clinical examination
  + Physical examination
  + Vital signs: resting systolic and diastolic blood pressure, pulse and temperature
  + Check of change of concomitant therapies/ medication since last visit
* Laboratory
* Efficacy assessments
  + Lichen Planus Activity and Damage Index (LiPADI) Activity Score
* Occurrence of AEs/SAEs
* Drug accountability
* Drug dispensation

OLE–V2 (Day 224 ± 3 days)

The following assessments and procedures will be performed at this visit:

* Clinical examination
  + Physical examination
  + Vital signs: resting systolic and diastolic blood pressure, pulse and temperature
  + Check of change of concomitant therapies/ medication since last visit
* Laboratory
  + RLab
* Efficacy assessments
  + Lichen Planus Activity and Damage Index (LiPADI) Activity Score
  + Dermatological Quality of Live Index (DLQI)
  + Numeric rating scale (NRS) for average itch during the past 24 hours
  + Photographic documentation of skin condition (only in Bonn)
* Occurrence of AEs/SAEs
* Drug accountability
* Drug dispensation

OLE–V3 (Day 336 ± 3 days)

The following assessments and procedures will be performed at this visit:

* Clinical examination
  + Physical examination
  + Vital signs: resting systolic and diastolic blood pressure, pulse and temperature
  + Change of concomitant therapies/ medication since last visit
* Laboratory ♣ RLab
  + Lab for mRNA-based gene expression analyses
* Skin sampling: A tape strip is taken from two defined areas of skin (lesional and non-lesional) on each patient
* Efficacy assessments
  + Lichen Planus Activity and Damage Index (LiPADI) Activity Score
  + Dermatological Quality of Live Index (DLQI)
  + Numeric rating scale (NRS) for average itch during the past 24 hours
  + Photographic documentation of skin condition (only in Bonn)
* Occurrence of AEs/SAEs
* Drug accountability
  + - 1. Safety Follow up

Safety –FU (30 days + 5 days after last IMP dosing)

* Clinical examination
  + Physical examination
  + Vital signs: resting systolic and diastolic blood pressure, pulse and temperature
  + Change of concomitant therapies/ medication since last visit
* Laboratory
  + RLab
* Efficacy Assessments
  + Lichen Planus Activity and Damage Index (LiPADI) Activity Score
  + Dermatological Quality of Live Index (DLQI)
  + Numeric rating scale (NRS) for average itch during the past 24 hours
  + Photographic documentation of skin condition (only in Bonn)
* Return of the diary
* Occurrence of AEs/SAEs
  + - 1. Unscheduled Visits

If a subject returns to the clinic outside of the normal study visit windows due to check of clinically significant SLab/RLab values, AEs/SAEs, early study termination or other reasons, assessments will be made at the Investigator’s discretion. All study relevant unscheduled visit assessments will be recorded in the patient record.

* 1. Country/Region-Specific Differences

Not applicable.

* 1. Prior Protocol Amendment(s)

This protocol has been amended previously. The Protocol Amendment Summary of Changes for the current amendment is located directly before the Table of Contents. Prior amendment(s) to this protocol are listed in the table below, beginning with the most recent.

|  |  |  |
| --- | --- | --- |
| **Document** | **Sponsor Approval Date (dd/mmm/yyyy)** |  |
| 2.0 | 28/JUL/2023 |  |
| Original Protocol | 26/JUL/2023 |  |

The Overview of Changes from each prior protocol amendment is provided below.

Amendment 2.0 28-AUG-2023

Correction of EU CT number

Specification throughout the document that only the Activity Score of the LiPADI index will be evaluated (incl. exchange of Figure 2 in chapter 21)

Chapters 1 and 9.2: Specification of inclusion criterion 5, respecting also patients with mucosal involvement only

Chapter 9.6: Adaption of strata, respecting also patients with oral involvement only Chapter 1, 4 and 8.3: Change in number of trial sites from 3 to minimum 3.

1. Appendix: Glossary of Terms and Abbreviations

Term Definition

§ Paragraph

% Percent

°C Celsius

°F Fahrenheit

< Smaller

≥ Greater or equal to

AE Adverse Event

AESI Adverse Events of Special Interest

ALT/GPT Alanine transaminase / glutamate pyruvate transaminase

AMG Arzneimittelgesetz (German Medicines Law)

A(D)R Adverse (Drug) Reaction

AP Alkaline phosphatase

Art. Article

ASR Annual Safety Report

AST/GOT Aspartate transaminase / glutamic oxaloacetic transaminase

AxIMP Auxiliary Medicinal Products

BOB Bundesoberbehörde (highest competent authority in Germany)

BOS Begin of Study

BfArM Bundesinstitut für Arzneimittel und Medizinprodukte

BLyS B lymphocyte stimulator, also called BAFF (B-cell activating factor)

BMI Body-mass-index

BMS Bristol-Myers Squibb

bpm Beats per minute

BSC Blood serum chemistry

CA Competent Authority

CBC Complete Blood Count

CCL Chemokine (C-C motif) ligand

CDMS Clinical Data Management System

CI Coordinating Investigator

CK Creatine kinase cm Centimeter

CRA Clinical Research Associate

(e)CRF (electronic) Case Report Form

CRO Contract Research Organization

CPK Creatine phosphokinase

CTR Clinical Trial Regulation

CTIS Clinical Trial Information System

CXCL Chemokine (C-X-C motif) ligand

D Deutschland (Germany)

DDI Drug-drug interaction

DILI Potential Drug Induced Liver Injury

DLQI Dermatology Life Quality Index

DP Double-blind Phase

DSMB Data Safety Monitoring Board

EC Ethics Committee

EDC Electronic Data Capture

EDTA Ethylenediaminetetraacetic acid e.g. Exempli gratia (for example)

EOS End of Study

EOT End of Treatment

et al. et alii (Latin for “and others”)

EU European Union

FAS Full Analysis Set

FDA United States Food and Drug Administration

FPFV First Subject First Visit

FPI First Patient In

FU Follow Up

GAS Global Assessment Score

GCP Good Clinical Practice

GDPR General Data Protection Regulation (EU) 2016/679

GFR Glomerular Filtration Rate

β-hCG (beta) Human chorionic gonadotrophin

HCT Hematocrit

HIV Human immunodeficiency virus

hrs Hours

IB Investigators Brochure

ICH International Conference on Harmonization

ID Identification number i.e. id

est (Latin for “this is”)

IFN Interferon

IMBIE Institute of Medical Biometry, Informatics and Epidemiology

I(M)P Investigational (Medicinal) Product

(s)IMPD (simplified) Investigator Medicinal Product Dossier

incl. inclusive

INR International Normalized Ratio

ISF Trial site File

ITT Intention-to-treat

IUD Intrauterine device

IUS Intrauterine system

IWRS Interactive Web Response System

JAK Janus kinase

K Kalium (Potassium)

kg kilogram

LiPADI Lichen Planus Activity and Damage Index

LPLV Last Patient Last Visit

LPO Last Patient Out

LTFU Lost to Follow-up

MCHC Mean corpuscular hemoglobin concentration

MCV Mean corpuscular volume

mg Milligram

mg/day Milligram per day

mg/dL Milligram per decilitre

mL Milliliter

mL/min Milliliter per minute

mmHg Millimeters of mercury

MxA Human myxovirus resistance protein 1

NCA National competent authorities

N Number

n.a. Not applicable

Na Natrium (Sodium)

No./Nr. Number

NRS Numeric Rating Scale

OLE Open label extension

ORBIS Hospital documentation system

PI Principal Investigator

PP Per protocol

PQC Product Quality Complaints

PSO Psoriasis

QTF QuantiFERON-TB Gold

RLab Routine lab

(m)RNA Messenger ribonucleic acid

SAE Serious Adverse Event

SAP Statistical Analysis Plan

SAR Serious Adverse Reaction

SC Short check-up

SDP Sponsor Delegated Person

SDV Source data verification

SFU Safety Follow-Up

SLab Screening lab

SMP Safety Management Plan

SOC Standard of Care

SOP Standard Operating Procedure

STAT Signal Transducer and Activator of Transcription

SUSAR Suspected Unexpected Serious Adverse Reaction

SZB Study Center Bonn (Studienzentrum Bonn)

Tbc Tuberculosis

TG Triglycerides

TMF Trial Master File

TRAIL TNF-Related Apoptosis Inducing Ligand

TYK Tyrosine kinase

UA(D)R Unexpected Adverse (Drug) Reaction

ULN Upper limit of normal

U.S. United States (of America)

V Visit

vs. versus

WCBP Women of childbearing potential

WHO World Health Organization

1. Appendix: References

Armstrong, April W.; Gooderham, Melinda; Warren, Richard B.; Papp, Kim A.; Strober, Bruce; Thaçi, Diamant et al. (2022): Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial. In: Journal of the American Academy of Dermatology. DOI: 10.1016/j.jaad.2022.07.002.

Boch, Katharina; Langan, Ewan A.; Kridin, Khalaf; Zillikens, Detlef; Ludwig, Ralf J.; Bieber, Katja (2021): Lichen Planus. In: Frontiers in medicine 8, S. 737813. DOI: 10.3389/fmed.2021.737813.

Chimalakonda, Anjaneya; Burke, James; Cheng, Lihong; Catlett, Ian; Tagen, Michael; Zhao, Qihong et al. (2021): Selectivity Profile of the Tyrosine Kinase 2 Inhibitor Deucravacitinib Compared with Janus Kinase 1/2/3 Inhibitors. In: Dermatology and therapy 11 (5), S. 1763–1776. DOI: 10.1007/s13555-021-00596-8.

Danese, Silvio; Peyrin-Biroulet, Laurent (2021): Selective Tyrosine Kinase 2 Inhibition for Treatment of Inflammatory Bowel Disease: New Hope on the Rise. In: Inflammatory bowel diseases 27 (12), S. 2023–2030. DOI: 10.1093/ibd/izab135.

Jo, Christine E.; Gooderham, Melinda; Beecker, Jennifer (2022): TYK 2 inhibitors for the treatment of dermatologic conditions: the evolution of JAK inhibitors. In: International journal of dermatology 61 (2), S. 139–147. DOI: 10.1111/ijd.15605.

Liu, Chunjian; Lin, James; Langevine, Charles; Smith, Daniel; Li, Jianqing; Tokarski, John S. et al. (2021): Discovery of BMS-986202: A Clinical Tyk2 Inhibitor that Binds to Tyk2 JH2. In: Journal of medicinal chemistry 64 (1), S. 677–694. DOI: 10.1021/acs.jmedchem.0c01698.

Mease, Philip J.; Deodhar, Atul A.; van der Heijde, Désirée; Behrens, Frank; Kivitz, Alan J.; Neal, Jeffrey et al. (2022): Efficacy and safety of selective TYK2 inhibitor, deucravacitinib, in a phase II trial in psoriatic arthritis. In: Annals of the rheumatic diseases 81 (6), S. 815–822. DOI: 10.1136/annrheumdis-2021-221664.

Morand, Eric; Pike, Marilyn; Merrill, Joan T.; van Vollenhoven, Ronald; Werth, Victoria P.; Hobar, Coburn et al. (2022): Deucravacitinib, a Tyrosine Kinase 2 Inhibitor, in Systemic Lupus Erythematosus: A Phase II, Randomized, Double-Blind, Placebo-Controlled Trial. In: Arthritis & rheumatology (Hoboken, N.J.). DOI: 10.1002/art.42391.

Stepien, Katarzyna; Zabska, Ewa; Rahnama-Hezava, Mansur; Reich, Adam (2022): Lichen Planus Activity and Damage Index (LiPADI)—Creationof the Questionnaire. In:Journal of Clinical Medicine 11 (1): 23. DOI: 10.3390/jcm11010023.

Strober, Bruce; Thaçi, Diamant; Sofen, Howard; Kircik, Leon; Gordon, Kenneth B.; Foley, Peter et al. (2022): Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, phase 3 POETYK PSO-2 trial. In: Journal of the American Academy of Dermatology. DOI: 10.1016/j.jaad.2022.08.061.

Sugerman, P. B.; Satterwhite, K.; Bigby, M. (2000): Autocytotoxic T-cell clones in lichen planus. In: The British journal of dermatology 142 (3), S. 449–456. DOI: 10.1046/j.1365-2133.2000.03355.x.

Wenzel, Joerg; Scheler, Marina; Proelss, Julia; Bieber, Thomas; Tüting, Thomas (2006): Type I interferon-associated cytotoxic inflammation in lichen planus. In: Journal of cutaneous pathology 33 (10), S. 672–678. DOI: 10.1111/j.1600-0560.2006.00527.x.

Wenzel, Joerg; Tüting, Thomas (2008): An IFN-associated cytotoxic cellular immune response against viral, self-, or tumor antigens is a common pathogenetic feature in "interface dermatitis". In: The Journal of investigative dermatology 128 (10), S. 2392–2402. DOI: 10.1038/jid.2008.96>