**A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Evaluate the Efficacy and Safety of RIST4721 in Subjects with Palmoplantar Pustulosis**

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**Protocol RIST4721-201 Version 3.0**

**Inclusion Criteria**

In order to be eligible to participate in this study, a subject must meet all of the following criteria at the screening and Day –1 visits, unless specified otherwise:

1. Male or female subject, aged 18–70 years at the time of consent.
2. Subject has at least a 6‑month history of PPP as defined by the presence of pustules on palms and/or soles, but without evidence of infection on palms and soles (information obtained from medical chart or subject’s physician, or directly from the subject).
3. Subject has moderate or severe PPP, as defined by PPPASI ≥8 and PPPGA ≥3 at Day –1, and a minimum of 8 fresh pustules at screening (fresh pustule count on both right/left palms and soles) and 20 fresh pustules at Day –1 (fresh pustule count on both right/left palms and soles).
4. Subject who wants to use an emollient should agree to use the same emollient, at the same frequency of application for 7 days before Day –1 and throughout the study. Note: However, on the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.
5. For female subject of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method, from at least 4 weeks before Day –1 until at least 4 weeks after the last study drug administration. Highly effective contraceptive methods include hormonal contraceptives (combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, male partner(s) vasectomy, tubal ligation, or a double‑barrier method of contraception (barrier methods include male condom, female condom, cervical cap, diaphragm, and contraceptive sponge) in conjunction with spermicide.

Note: Subjects who are on hormonal contraceptive must have been on a stable dose for at least 4 weeks before Day –1.

Note: The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day –1 and will continue to be abstinent from penile‑vaginal intercourse throughout the study. 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 participant.

Note: For countries where double-barrier methods are not accepted as highly effective contraception, then this option must not be considered.

Note: A female of nonchildbearing potential is defined as follows:

* Female who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).
* Female who has had a cessation of menses for at least 12 months without an alternative medical cause, and a FSH test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).
1. Female subject of childbearing potential has a negative serum pregnancy test at screening and negative urine pregnancy test at Day –1.
2. Female subject agrees to not have egg retrieval during the study and for 1 month after the last study drug administration.
3. Male subject agrees to use condom and spermicide from Day –1 until at least 3 months after the last study drug administration.
4. Male subject agrees not to donate sperm during the study and for 3 months after the last study drug administration.
5. Subject has negative TB infection test. Subject will be evaluated for latent TB infection with a PPD test or a QuantiFERON-TB Gold test, if one has not been performed in the last 6 months. Subjects who demonstrate evidence of latent TB infection (either PPD ≥5 mm of induration or positive QuantiFERON-TB Gold test, irrespective of bacille Calmette‑Guérin vaccination status) will not be allowed to participate in the study. Subjects with documented completed treatment for latent TB will be allowed to participate in the study without retesting.
6. Subject is willing to participate and is capable of giving informed consent. Note: Consent must be obtained prior to any study-related procedure.
7. Subject must be willing to comply with all study procedures and must be available for the duration of the study.

**Exclusion Criteria**

A subject who meets any of the following criteria at the screening and Day –1 visits, unless specified otherwise, will be excluded from participation in this study:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. Subject has evidence of erythrodermic, generalized pustular psoriasis, predominantly guttate psoriasis, or drug-induced psoriasis.
3. Subject has a history of skin disease or presence of skin condition (except psoriasis) that, in the opinion of the investigator, would interfere with the study assessments.
4. Subject has moderate to severe psoriasis, as defined by plaque psoriasis covering ≥10% of his/her total BSA at Day –1.
5. Subject is known to have immune deficiency or is immunocompromised.
6. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day –1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or successfully treated localized carcinoma in situ of the cervix are not to be excluded.
7. Subject had a major surgery within 8 weeks prior to Day –1 or has a major surgery planned during the study.
8. Subject has any clinically significant medical condition or ECG/physical/laboratory/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
9. Subject has positive results for HBsAg, antibodies to anti-HBc, HCV, or HIV.
10. Any clinically significant history of infection (except for localized herpes simplex) within 4 weeks prior to Day –1.
11. Subject has absolute neutrophil count <1.8 x 109/L at screening.
12. Subject has ALT, AST or total bilirubin values ≥2 times the ULN, or other clinical evidence of significant hepatic impairment (eg, ascites, peri-umbilical veins, oesophageal varices) at screening.
13. Subject has a history of clinically significant anemia or Hgb value ≤10 g/dL at screening.
14. Subject has a creatinine clearance ≤60 ml/min at screening (calculated with MDRD formula).
15. Subject has used any topical medication to treat PPP, including corticosteroids, retinoids, vitamin D analogues (such as calcipotriol), or tar within 2 weeks prior to Day –1.
16. Subject has used topical dapsone within 2 weeks prior to Day –1.
17. Subject has used any systemic treatment for PPP, including corticosteroids, oral retinoids, biotin, immunosuppressive medication, methotrexate, cyclosporine, colchicine or apremilast, within 4 weeks prior to Day –1. Note: Intranasal corticosteroids and inhaled corticosteroids for stable medical conditions are allowed if subject has been on a stable dose for at least 4 weeks prior to Day –1 and will agree to maintain the same dose for the duration of the study. Eye drops containing corticosteroids are allowed.
18. Subject has used strong systemic cytochrome P450 3A4/5 inhibitors or inducers within 4 weeks or 5 half-lives, whichever is longer, prior to baseline (Day –1) (topical cytochrome P450 3A4/5 inducers or inhibitors with known limited systemic availability may be permitted).
19. Subject has received any UV‑B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day –1.
20. Subject has had PUVA treatment within 4 weeks prior to Day –1.
21. Subject has received any marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day –1.
22. Subject is currently receiving a nonbiological investigational product or investigational device or has received one within 4 weeks prior to Day –1.
23. Subject had excessive sun exposure or has used tanning booths within 4 weeks prior to Day –1, or subject is planning a trip where excessive sun exposure is expected, or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when exposure cannot be avoided.
24. Subject has a known or suspected allergy to RIST4721 or any component of the study drug.
25. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day –1.
26. Close affiliation with the investigator (eg, a close relative), including any study staff of the sites or persons working at the CRO or subject is an employee of sponsor.
27. Subject is institutionalized because of legal or regulatory order.
28. For subjects consenting to biopsies only:
* Subject has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics.
* Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites.
* Subject has taken anticoagulant medication, such as heparin, LMW heparin, warfarin, antiplatelets (except low-dose aspirin, which will be allowed), within 2 weeks prior to Day –1, or has a contraindication to skin biopsies. NSAIDs will not be considered antiplatelets and will be allowed.