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ORIGINAL RESEARCH

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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ABSTRACT

Introduction: Palmoplantar pustulosis (PPP) is a chronic inflammatory skin condition with neutrophilic infiltration of the epidermis. RIST4721 antagonizes CXC chemokine receptor type 2, which is important in neutrophil recruitment and migration. In this study, the efficacy and safety of RIST4721 versus placebo were assessed in adult subjects with moderate to severe PPP.

Methods: This phase 2a, multicenter, randomized, double-blind, placebo-controlled study investigated RIST4721 versus placebo in subjects with moderate to severe PPP. Key eligibility criteria included: Palmoplantar Pustulosis Area and Severity Index (PPPASI) ≥ 8 and Palmoplantar Pustulosis Physician Global Assessment ≥ 3. Subjects were randomized 1:1 to RIST4721 300 mg or placebo once daily for 28 days. The primary efficacy endpoints were relative change from baseline in fresh and total pustule count at day 28.

Results: Fifteen subjects received RIST4721 and 19 subjects received placebo. Treatment with RIST4721 was found to be generally well tolerated. At day 28, the mean ± standard deviation (SD) relative change from baseline in fresh pustule count was 0.86 ± 0.692 and 0.53 ± 0.561 ($P = 0.240$) and in total pustule count was 0.99 ± 0.667 and 0.96 ± 0.672 ($P = 0.804$) for RIST4721 and placebo groups, respectively. Subgroup analysis of subjects with progressing disease demonstrated that subjects with a PPPASI-50 at day 28 was significantly higher for subjects treated with RIST4721 (71%) than placebo (15%) ($P = 0.022$).

Conclusion: Preliminary data suggest RIST4721 is well tolerated and may be a potential therapy for patients with PPP.

Trial Registration: RIST4721-201 was registered in June 2019 at clinicaltrials.gov: NCT03988335.

Keywords: RIST4721; Palmoplantar pustulosis; Pustules; Neutrophils; CXCR2

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13555-021-00632-7.

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Key Summary Points
Why carry out this study?
Oral and topical treatment options for palmoplantar pustulosis have poor evidence of benefit. These current options include super-potent corticosteroids, phototherapy, acitretin, methotrexate, and cyclosporine
RIST4721 is a potent CXCR2 antagonist that blocks neutrophil influx to sites of inflammation, which was compared to placebo in a 4-week, double-blind manner
What was learned from this study?
RIST4721 was not significantly superior to placebo at 4 weeks. Subgroup analysis of patients with active disease demonstrated a potential for efficacy with RIST4721
RIST4721 was generally well tolerated
Further evaluation of RIST4721 as a potential therapy is warranted

INTRODUCTION

Palmoplantar pustulosis (PPP) is a rare, chronic inflammatory skin condition characterized by sterile pustules with erythema, hyperkeratosis, scaling, pruritus, pain, and/or burning sensation on the palms and soles [1–3]. Pustular lesions may also extend to the subject's wrists and heels [2]. The clinical manifestations of PPP make it a debilitating condition that puts the afflicted subjects at risk of social stigmatism and reduced quality of life [4].

PPP is commonly diagnosed in females between 40 and 69 years of age and in individuals who are current or former smokers [5, 6]. There is a strong association between smoking and PPP; however, the exact pathobiology remains unclear [3].

Several hypotheses have been proposed to explain neutrophil recruitment in PPP. One notably suggests human cathelicidin antimicrobial peptide, hCAP-18, and its processed forms, LL-37 and TLN-58, are found in vesicles that develop into pustules [7]. These data are consistent with the findings that suggest there is a microbiome within the pustules and vesicles of subjects with PPP [8]. Furthermore, hCAP-18 is potentially responsible for the potentiation of PPP through the upregulation of pro-inflammatory cytokines including interleukin (IL) 8, IL-23, IL-17C, IL-1α, and IL-1β in surrounding lesional keratinocytes [9]. IL-8 is implicated in many inflammatory diseases involving neutrophil migration and activation; thus, it may be a key player in the pustulation of PPP [10, 11]. These findings are consistent with the significant neutrophilic infiltration of the epidermis observed in patients with PPP.

There are currently no treatments approved for PPP in the USA, Canada, and the European Union; thus, off-label topical and systemic treatments are often used. Guselkumab has been proven to be effective in PPP as well as pustulotic arthro-osteitis and is approved for use in Japan [12, 13]. Off-label topical therapies including corticosteroids, calcipotriene, psoralen and ultraviolet A, and tacrolimus often have limited efficacy in PPP due to the lower relative absorptive capacity of the palms and soles compared to other body areas [2, 14, 15]. Off-label systemic treatments including acitretin, cyclosporine, colchicine, and biologic agents (e.g., IL-23, IL-17 antagonists) have limited efficacy and can be associated with significant side effects [2, 16, 17]. The lack of approved targeted treatments for PPP warrants the development of a more efficacious option.

CXC chemokine receptor type 2 (CXCR2) inhibitors block CXCR2 ligands, including IL-8, preventing neutrophil migration to sites of inflammation; therefore, the blockade of CXCR2 may represent a novel therapeutic approach for the treatment of neutrophil-mediated inflammatory disorders, including PPP [18].

RIST4721 is a small molecule CXCR2 antagonist with potential as a novel oral treatment for neutrophilic-mediated diseases, including PPP. RIST4721 has demonstrated a 134- and 47-fold greater selectivity for CXCR2 than CXC

chemokine receptor type 1 (CXCR1) and CC chemokine receptor type 2b (CCR2b), respectively; thus, it is a high-potency CXCR2 antagonist that prevents neutrophil egress [19]. Due to its minimal activity on CXCR1, RIST4721 does not affect neutrophil activation [20]. Since RIST4721 inhibits the binding of ligands, including IL-8, on CXCR2, its on-target effect results in the reduction of absolute neutrophil count (ANC).

Prior phase 1 studies have shown that RIST4721 is generally well tolerated with dose-dependent and reversible reductions in ANCs.

Here we report the results from a phase 2a study that investigated the efficacy and safety of RIST4721 versus placebo in subjects with moderate to severe PPP.

METHODS

Study Design and Participants

This exploratory phase 2a, multicenter, randomized, double-blind, placebo-controlled study was approved by the Ethics Committees and Institutional Review Boards of participating centers in Canada (12 sites) and Germany (5 sites) (refer to the Supplementary Material [S3] for the full list of Institutional Review Boards and Ethics Committees consulted during the study). The study was conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines. Written informed consent was obtained from all individual participants included in the study.

Eligibility criteria included the following: subjects 18–70 years of age; ≥ 6-month history of PPP as defined by the presence of pustules on palms and/or soles, but without evidence of infection; moderate or severe PPP as defined by Palmoplantar Pustulosis Psoriasis Area and Score Index (PPPASI) ≥ 8 and Palmoplantar Pustulosis Physician Global Assessment (PPPGA) ≥ 3 at day-1 (day prior to study drug administration); and a minimum of 8 fresh pustules at screening and 20 fresh pustules at day-1. Fresh pustules were defined as macroscopically visible pustules that were white/yellow in color with no brown color, with or without crust, and present on the glabrous skin of the palms and/or soles. Inclusion/exclusion criteria are further described in the supplementary material (S1).

Eligible subjects were randomized in a 1:1 ratio to receive either RIST4721 or placebo using a generated randomization list, which was uploaded to an Interactive Web Response System. Randomization was stratified by consent to skin biopsy collection.

The duration of this study included an up to 30-day screening period, 1 day for eligibility confirmation and randomization, a 28-day treatment period, and a 14-day follow-up period.

Study Treatments and Assessments

RIST4721 300 mg or placebo solution was administered orally once daily for 28 days. A once-daily product administration was chosen since pharmacokinetic data collected in phase 1 clinical studies supported a single daily dose administration [21]. Based on modeling of phase 1 peripheral neutrophil counts, the dose of 300 mg was chosen because it was unlikely to cause moderate or severe neutropenia.

To monitor the disease progression of PPP, the following assessments were performed at baseline and at study visits: fresh and total pustule counts, PPPASI, PPPGA, Palmoplantar Pustulosis Severity Index (PPSI), pain visual analogue scale (VAS), and Dermatology Life Quality Index (DLQI) [22–27].

Blood samples for the assessment of RIST4721 plasma concentrations were collected on days 7 and 21 from a subgroup of subjects who consented in both the RIST4721 (n = 9) and placebo (n = 8) treatment groups.

Safety was assessed with physical examinations, vital signs, electrocardiograms, clinical laboratory tests, and collection of adverse events (AEs) throughout the duration of the study. AEs were coded according to the Medical Dictionary for Regulatory Activities, Version 21.1. Smoking status and changes in smoking status were collected from all subjects from

randomization through the study follow-up period.

Early termination or follow-up assessments were performed 14 days after last administration of study drug.

Endpoints

Relative changes from baseline in fresh and total pustule counts at day 28 were the primary efficacy endpoints. Absolute change from baseline in fresh and total pustule counts at day 28 and proportion of subjects achieving at least a 50% reduction in fresh and total pustule counts at day 28 were the secondary efficacy endpoints.

Notable exploratory endpoints included the proportion of subjects achieving at least a 50% reduction in PPPASI (PPPASI-50) and PPSI at each visit and plasma concentrations of RIST4721.

Statistical Analysis

The data analysis utilized the modified intent-to-treat (mITT) population, which was defined as all subjects who received at least one dose of the study drug. This was the primary analysis set for efficacy.

The safety analysis included all subjects who received at least one dose of the study drug. This analysis set was used to summarize data including demographic and other baseline characteristics, exposure, and safety.

The plasma concentration analysis included all subjects who received at least one dose of study drug and had plasma concentration data. The pharmacodynamic analysis set included all subjects who received at least one dose of study drug and who had an assessment of pharmacodynamic parameters.

A mixed model repeated measures model was used for analyzing the following: absolute and relative change from baseline in fresh and total pustule counts, PPPASI, pain VAS, and DLQI. Each endpoint was transformed for each treatment group and each visit separately using McCune et al. generalized natural log transformation [28]. The model included treatment, visit (day 7, day 14, day 21, and day 28), and treatment-by-visit interaction as fixed effect and natural log of baseline value as covariate. Unstructured covariance was used to model the correlation. If convergence issues arose, the autoregressive (AR [1]) structure was used.

Differences in dichotomic response endpoints between treatment groups at day 28 were analyzed using a Fisher's exact test. A 90% CI for the treatment difference in response was also provided (exact unconditional confidence limits).

Post hoc analyses of PPPASI-50 and target palm or sole pustule count in subjects with progressing disease from screening to baseline were conducted utilizing a *t*-test.

Patient Population

Thirty-five subjects with moderate to severe PPP were enrolled and randomized to RIST4721 or placebo; however, only 34 subjects received at least one dose of study drug. Twenty-eight (82.4%) subjects in the study were female. Twenty-five (73.5%) subjects were current smokers and 5 (14.7%) subjects had a history of smoking, which is consistent with the literature (Table 1) [22, 29]. Smoking history was similar across treatment groups. At baseline, the mean ± standard deviation (SD) fresh pustule count was 33.5 ± 17.99 and the mean ± SD total pustule count was 92.8 ± 76.88 (Table 2). All subjects had PPPASI ≥ 8 and PPPGA ≥ 3 and were also assessed for PPPASI, PPPGA, PPSI, and PPP history at baseline (Table 3).

RESULTS

Exposure

Of the 35 subjects randomized to RIST4721 300 mg or placebo oral solution, 34 subjects received at least one dose of study drug, and 32 subjects completed the study (Fig. 1). One subject in the RIST4721 group did not receive the first dose of RIST4721 and was lost to follow-up. Fifteen subjects received RIST4721 300 mg and 19 subjects received placebo. Subjects in both groups, two subjects in the RIST4721

Table 1 Patient demographics and baseline characteristics

Characteristics	RIST4721 *n* = 15	Placebo *n* = 19	Total *n* = 34
Age (years)			
Mean (SD)	50.5 (11.22)	50.0 (12.27)	50.2 (11.64)
Median (IQR)	53.0 (17.0)	55.0 (19.0)	55.0 (18.0)
Gender, *n* (%)			
Female	12 (80.0)	16 (84.2)	28 (82.4)
Male	3 (20.0)	3 (15.8)	6 (17.6)
Baseline smoking status, *n* (%)			
Current smoker	11 (73.3)	14 (73.7)	25 (73.5)
Former smoker	3 (20.0)	2 (10.5)	5 (14.7)
Non-smoker	1 (6.7)	3 (15.8)	4 (11.8)

IQR interquartile range, *SD* standard deviation

Table 2 Baseline pustule count

Characteristics	Baseline fresh pustule count			Baseline total pustule count		
	RIST4721 *n* = 15	Placebo *n* = 19	Total *n* = 34	RIST4721 *n* = 15	Placebo *n* = 19	Total *n* = 34
Total count						
Mean (SD)	29.7 (9.69)	36.6 (22.32)	33.5 (17.99)	93.1 (81.51)	92.6 (75.28)	92.8 (76.88)
Median (IQR)	27.0 (17.0)	26.0 (25.0)	26.5 (15.0)	74.0 (72.0)	54.0 (85.0)	60.0 (69.0)

IQR interquartile range, *SD* standard deviation

group and three subjects in the placebo group, had significant increases or decreases in their smoking status or frequency over the course of the treatment period. Additionally, none of the subjects enrolled in the study had a medical history of pustulotic arthro-osteitis.

Pharmacokinetics and Safety

Pre- and postdose assessments demonstrated measurable plasma concentrations of RIST4721 but not placebo at day 7 and day 21.

Treatment with RIST4721 demonstrated more subjects in the RIST4721 group (86.7%, *n* = 13; 39 events) compared to the placebo group (36.8%, *n* = 7; 12 events) experienced treatment-emergent AEs (TEAEs). Most TEAEs were mild in severity and were related to gastrointestinal or musculoskeletal and connective tissue disorders and had resolved at the time of study completion (Table 4). The most frequent gastrointestinal AE was diarrhea with five subjects on RIST4721 and one subject on placebo. No subjects discontinued treatment because of gastrointestinal-related AEs.

The mean ± SD ANC decreased but remained within the reference range between baseline (4.041 ± 1.1703 10E9/l) and day 28 (2.499 ± 0.9059 10E9/l) in the RIST4721 group. No corresponding decrease in ANC was

Table 3 Baseline disease characteristics

Characteristics	RIST4721 *n* = 15	Placebo *n* = 19	Total *n* = 34
Baseline PPPASI total			
Mean (SD)	17.61 (9.084)	20.05 (7.509)	18.98 (8.202)
Median (IQR)	14.30 (15.00)	18.20 (11.90)	17.40 (12.80)
Baseline PPPGA			
3—Moderate, *n* (%)	13 (86.7)	14 (73.7)	27 (79.4)
4—Severe, *n* (%)	2 (13.3)	5 (26.3)	7 (20.6)
Mean (SD)	3.1 (0.35)	3.3 (0.45)	3.2 (0.41)
Median (IQR)	3.0 (0.0)	3.0 (1.0)	3.0 (0.0)
Baseline PPSI total			
Mean (SD)	8.5 (1.30)	9.2 (1.34)	8.9 (1.35)
Median (IQR)	9.0 (3.0)	9.0 (2.0)	9.0 (2.0)
PPP history			
Location, *n* (%)			
Palms and soles	9 (60.0)	15 (78.9)	24 (70.6)
Soles	6 (40.0)	4 (21.1)	10 (29.4)
Psoriasis elsewhere on the body, *n* (%)			
No	10 (66.7)	12 (63.2)	22 (64.7)
Yes	5 (33.3)	7 (36.8)	12 (35.3)

Baseline was defined as the last nonmissing assessment prior to the first dose of study treatment
IQR interquartile range, *PPP* palmoplantar pustulosis, *PPPASI* Palmoplantar Pustulosis Psoriasis Area and Severity Index, *PPPGA* Palmoplantar Pustulosis Physician Global Assessment, *PPSI* Palmoplantar Pustulosis Severity Index, *SD* standard deviation

observed in the placebo group (5.171 10E9/l at baseline and 5.498 10E9/l at day 28). The absolute change in neutrophils from baseline is shown in Fig. 2.

Two subjects in the RIST4721 group experienced TEAEs of neutropenia that were mild, transient, and asymptomatic. In both cases, the AEs did not lead to treatment discontinuation and the ANC returned to normal by day 42 (Table 5). Neither subject recorded an ANC of < 1.0 10E9/l at any time point.

Efficacy

In the mITT analysis set, 34 subjects were included in the efficacy analysis.

There were no statistically significant differences between RIST4721 and placebo for primary efficacy endpoints. The mean ± SD relative change from baseline in fresh pustule count at day 28 was 0.86 ± 0.692 for the RIST4721 group and 0.53 ± 0.561 for the placebo group ($P = 0.240$). The mean ± SD relative change from baseline in total pustule count at day 28 was 0.99 ± 0.667 for the RIST4721 group

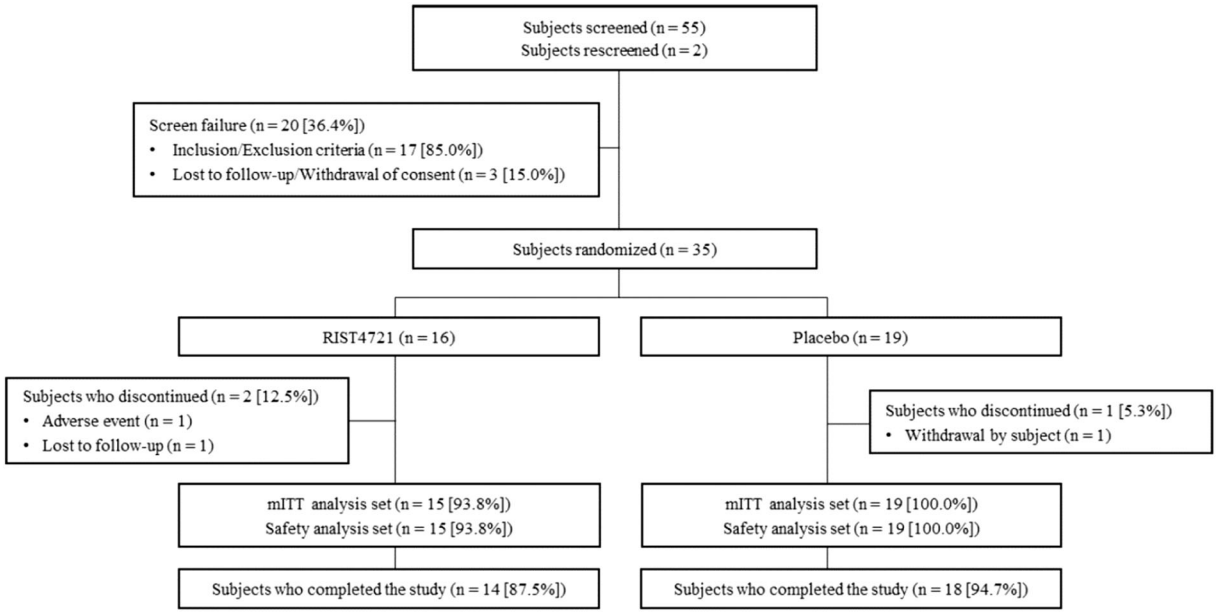

Fig. 1 CONSORT diagram. *mITT* modified intent to treat

and 0.96 ± 0.672 for the placebo group (P = 0.804) (Figs. 3 and 4).

There were no statistically significant differences between RIST4721 and placebo groups in the fresh and total pustule counts (P = 0.616), apart from absolute change from baseline in fresh pustule count at day 28. The decrease in fresh pustule count observed between baseline and day 28 resulted in a mean ± SD absolute change from baseline of – 2.1 ± 19.68 for the RIST4721 group and – 18.3 ± 24.05 for the placebo group (P = 0.053).

The number and proportion of subjects who achieved a 50% reduction in fresh pustule count at day 28 were 57.9% (n = 11) of subjects in the placebo group compared to 40% (n = 6) of subjects in the RIST4721 group. Comparison of the two groups revealed no statistically significant differences (P = 0.491).

An analysis of the PPPASI score over time revealed that it progressively decreased from baseline to day 28 in both treatment groups. The mean ± SD absolute change from baseline was – 7.7 ± 5.75 and – 7.6 ± 6.23 for the RIST4721 and placebo groups, respectively (P = 0.470). The mean ± SD relative change from baseline in PPPASI score at day 28 was also similar between the RIST4721 (0.58 ± 0.216) and placebo (0.64 ± 0.280) groups (P = 0.713).

A numerically higher proportion of subjects achieved PPPASI-50 in the RIST4721 group (40%, n = 6) compared to placebo (26.3%, n = 5) at day 28; however, no statistically significant differences between treatment groups were observed (P = 0.475).

The PPSI change from baseline was similar at day 28 for RIST4721 (– 1.91 ± 0.483) and placebo (– 1.98 ± 0.548). Evaluation of the subscores of erythema, pustules, and desquamation demonstrated greater numerical changes in the least square mean (standard error) for erythema and desquamation subscores with RIST4721 (Table 6).

An analysis of the number and proportion of subjects in each PPPGA category over time revealed a similar pattern of response in both treatment groups with an overall decrease in PPPGA scores from baseline to day 28 (Table 7).

The intensity of pain experienced by subjects decreased between baseline and day 28 in both treatment groups, although the pain VAS scores were numerically higher in the placebo group compared to the RIST4721 group at all study visits. The mean ± SD absolute changes from

Table 4 Summary of treatment-emergent adverse events by system organ class

System organ class	RIST4721 *n* = 15 *n* (%)	Placebo *n* = 19 *n* (%)
Subjects with at least one TEAE	13 (86.7)	7 (36.8)
Gastrointestinal disorders	7 (46.7)	1 (5.3)
Musculoskeletal and connective tissue disorders	4 (26.7)	3 (15.8)
Infections and infestations	3 (20.0)[a]	1 (5.3)
Injury, poisoning, and procedural complications	2 (13.3)	2 (10.5)
Nervous system disorders	1 (6.7)	3 (15.8)
Renal and urinary disorders	3 (20.0)	1 (5.3)
Investigations	3 (20.0)	0
Blood and lymphatic system disorders	2 (13.3)	0

Treatment-emergent adverse events were defined as any condition that was not present prior to treatment with the study product but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated). Subjects experiencing multiple AEs within the same SOC were counted only once for that SOC. Similarly, subjects experiencing multiple AEs within the same PT were counted only once for that PT. Adverse events were coded using MedDRA version 21.1.

AE adverse event, *MedDRA* Medical Dictionary for Regulatory Activities, *PT* preferred term, *SOC* system organ class, *TEAE* treatment-emergent adverse event

[a] The subject (RIST4721) experienced a TEAE of mild post-procedural cellulitis (cellulitis around the biopsy site on the left foot) starting on day 1. The subject received beta-lactam antibacterials on day 7 for the management of this TEAE, which lasted 17 days and was judged as not related to treatment by the investigator

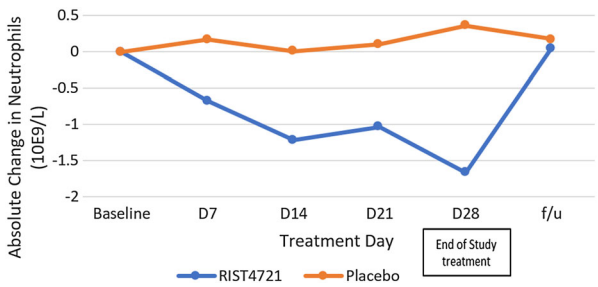

Fig. 2 Absolute change in neutrophils. *D* day, *f/u* follow-up

baseline between the RIST4721 (– 0.8 ± 3.30) and placebo groups (– 0.9 ± 3.55) were comparable ($P = 0.832$).

The DLQI score decreased from baseline to day 28 in both treatment groups. The mean ± SD absolute change from baseline in the placebo group was – 4.2 ± 6.44 compared to the RIST4721 group, which was – 1.9 ± 3.39 ($P = 0.392$). There was a comparable mean ± SD relative change from baseline in DLQI score at day 28 in the RIST4721 (0.68 ± 0.440) and placebo groups (0.60 ± 0.530) ($P = 0.527$).

In a post hoc analysis of subjects with progressing disease (defined as an increase in total pustule count between screening and baseline; $n = 7$ RIST4721, $n = 13$ placebo), the proportion of subjects with a PPPASI-50 at day 28 was significantly higher in subjects treated with RIST4721 (71%) than placebo (15%) ($P = 0.022$) (Fig. 5). Additionally, the proportion of subjects who achieved PPPASI-50 at any time through day 42 was numerically greater in RIST4721 than in the placebo group (Fig. 6). Improvement from baseline in pustule count of target

Table 5 Laboratory ANC parameters with clinically significant test results

	ANC (10E9/l)					
	Baseline	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 42**
Subject 1	2.24	1.08	1.44	1.56	1.64	2.88
Subject 2	2.59	2.35	2.31	1.53	1.21	2.88

Reference range 1.8–7.7 10E9/l. Baseline was defined as the last nonmissing assessment prior to the first study treatment application

ANC absolute neutrophil count

One subject in the RIST4721 group withdrew from the study drug and discontinued the study because of a TEAE of moderate anxiety (judged not related to the study drug), and one subject in the placebo group discontinued the study because of withdrawal of consent. There were no serious AEs or deaths reported in the study

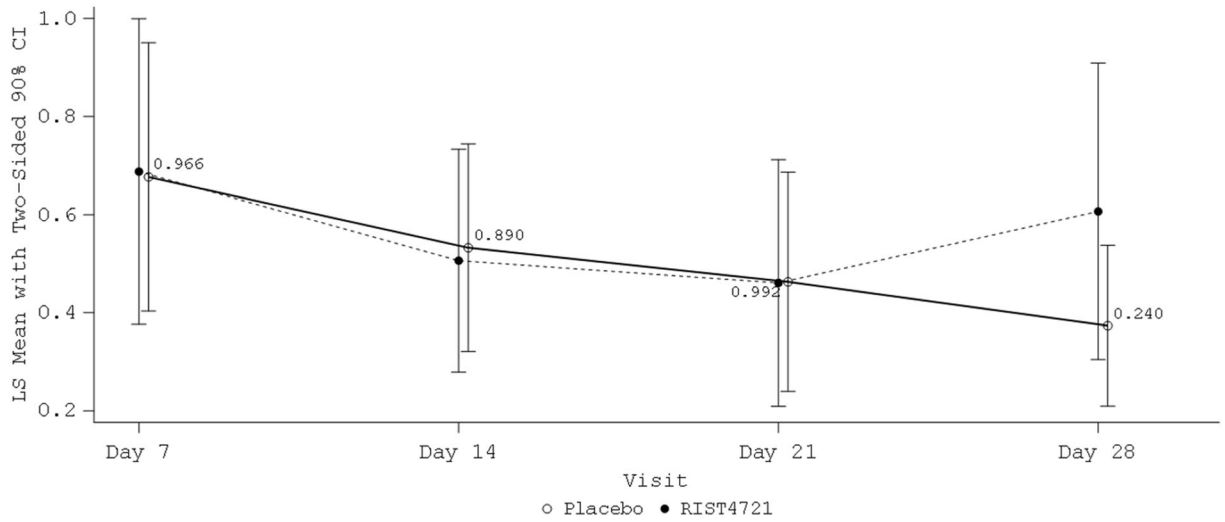

Fig. 3 Relative change from baseline in fresh pustule count by visit. LS means, two-sided 90% CIs, and *P*-values are from a MMRM analysis on relative change from baseline in fresh pustule count. The model includes treatment, visit (days 7, 14, 21, and 28), and treatment-by-visit interaction as fixed effects and the baseline value as covariate. *CI* confidence interval, *LS* least squares, *MMRM* mixed model for repeated measurements

palm or sole was significantly higher in subjects treated with RIST4721 (− 29.0 [31.52]) than placebo (− 3.5 [17.89]) ($P < 0.050$).

DISCUSSION

This phase 2a study aimed to assess the safety and efficacy of RIST4721 in subjects with active PPP. RIST4721 was well tolerated among subjects and clearly demonstrated its on-target effect by declines in absolute and relative neutrophil counts, which returned to baseline levels by day 42 while off treatment. The results also revealed that once daily oral treatment with RIST4721 300 mg solution demonstrated serum concentration levels consistent with previous studies with RIST4721 solution [20].

With respect to tolerability, the most frequently encountered TEAEs with RIST4721 were gastrointestinal disorders, which were predominantly mild in nature, and none of the subjects treated with RIST4721 discontinued the study

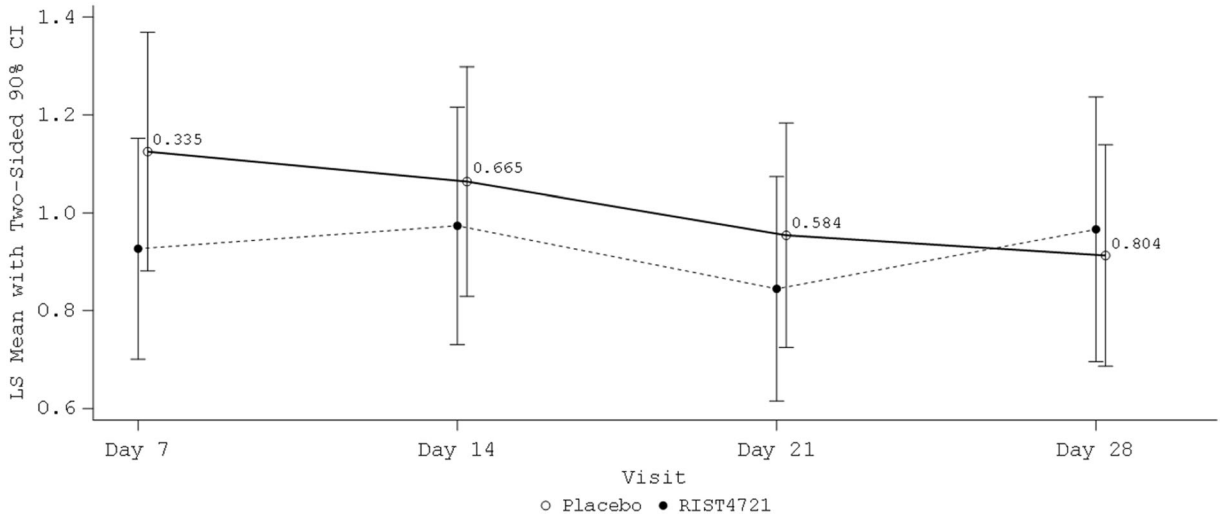

Fig. 4 Relative change from baseline in total pustule count by visit. LS means, two-sided 90% CIs, and *P*-values are from a MMRM analysis on relative change from baseline in total pustule count. The model includes treatment, visit (days 7, 14, 21, and 28), and treatment-by-visit interaction as fixed effects and the baseline value as covariate. *CI* confidence interval, *LS* least squares, *MMRM* mixed model for repeated measurements

Table 6 PPSI scores at day 28 (mITT analysis set)

Endpoint	Placebo *n* = 18	RIST4721 *n* = 14	Difference
	LS mean (SE)	LS mean (SE)	LS mean (SE)
Erythema score			
Day 28 observed value	2.23 (0.158)	2.07 (0.179)	–
Day 28 change from baseline	0.49 (0.158)	− 0.66 (0.179)	− 0.17 (0.239)
Pustule score			
Day 28 observed value	2.32 (0.205)	2.41 (0.233)	–
Day 28 change from baseline	− 0.74 (0.205)	− 0.66 (0.233)	0.08 (0.313)
Desquamation (scaling) score			
Day 28 observed value	2.43 (0.178)	2.30 (0.203)	–
Day 28 change from baseline	− 0.63 (0.178)	− 0.75 (0.203)	− 0.13 (0.274)
Total score			
Day 28 observed value	6.93 (0.483)	6.86 (0.548)	–
Day 28 change from baseline	− 1.91 (0.483)	− 1.98 (0.548)	− 0.07 (0.738)

LS least squares, *mITT* modified intent to treat, *PPSI* Palmoplantar Pustulosis Severity Index, *SE* standard error

Table 7 Summary and statistical analysis of PPPGA (mITT analysis set)

Visit category	RIST4721 *n* = 15 *n* (%)	Placebo *n* = 19 *n* (%)
Baseline		
Clear	0 (0.0)	0 (0.0)
Almost clear	0 (0.0)	0 (0.0)
Mild	0 (0.0)	0 (0.0)
Moderate	13 (86.7)	14 (73.7)
Severe	2 (13.3)	5 (26.3)
P-value[a]	0.426	–
Day 28		
Clear	0 (0.0)	0 (0.0)
Almost clear	1 (6.7)	1 (5.3)
Mild	4 (26.7)	6 (31.6)
Moderate	9 (60.0)	9 (47.4)
Severe	0 (0.0)	2 (10.5)
P-value[a]	0.711	–

mITT modified intent to treat, *PPPGA* Palmoplantar Pustulosis Physician Global Assessment

[a] *P*-value from a chi-square/Fisher's exact test

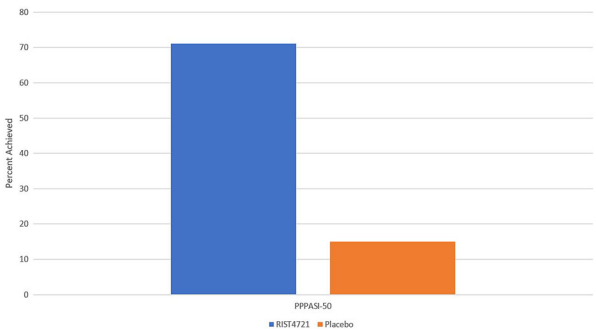

Fig. 5 Post hoc analysis of subgroup of subjects achieving PPPASI-50 at day 28. *T*-test analysis of subgroup of subjects with progressing disease who had an increase in total pustule count between screening and baseline. *PPPASI* Palmoplantar Pustulosis Psoriasis Area and Score Index, *PPPASI-50* 50% reduction in PPPASI

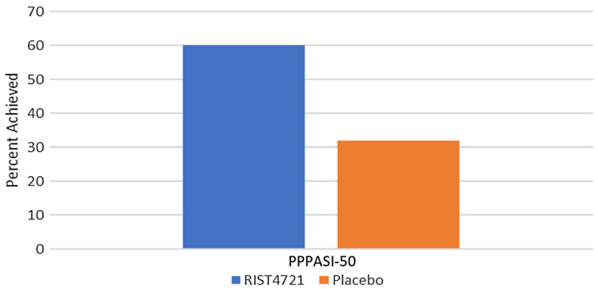

Fig. 6 Proportion of subjects achieving PPPASI-50 at any time. *T*-test analysis of the proportion of subjects was conducted. *PPPASI* Palmoplantar Pustulosis Psoriasis Area and Score Index, *PPPASI-50* 50% reduction in PPPASI

drug or study because of gastrointestinal AEs. A tablet formulation will be utilized in future clinical trials, which may improve the gastrointestinal tolerability of RIST4721.

Fresh pustule counts were selected as a measure to define subjects with active disease to observe the activity of RIST4721. However, given the limited number of ongoing research programs in PPP, there are limited data on pustule count endpoints. The mean fresh pustule counts recorded at each visit had high SDs, and the range of the datasets (minimum, maximum) was broad. Additionally, the number of fresh pustules counted on the palms and soles of a given subject varied greatly between sites and visits. Therefore, the enrolled study population may not have represented a homogeneous group of subjects with active disease.

Limited differences were observed in the primary and secondary efficacy endpoints as measured by fresh and total pustule counts between treatment groups. Given the observed high inter- and intra-subject variability, it is possible that counting observations related to fresh pustules was more difficult and more subjective than originally anticipated, which could have had a negative effect on the power of this small study.

PPP severity fluctuates with time, and many patients have periods of flare followed by periods of less active disease. Given this, a post hoc

analysis was conducted to exclude patients who were spontaneously improving between screening and randomization. This analysis demonstrated that the proportion of subjects with a PPPASI-50 at day 28 was significantly higher in subjects treated with RIST4721 (71%) than in those given placebo (15%) ($P = 0.022$) (Fig. 5). The differences observed in patients treated with RIST4721 with progressing disease may be an early indicator of the efficacy of RIST4721 in the prevention of new PPP flares and the blockage of concurrent PPP flares through the blockade of neutrophil migration to the skin. A longer treatment duration may demonstrate an effect on other efficacy parameters.

Additionally, these findings are consistent with the findings from a phase 2 study with spesolimab wherein no differences were observed between active therapy and placebo in the intent-to-treat population [30]. However, indicators of efficacy were observed in subjects not spontaneously improving between screening and baseline [30].

There were limitations related to this study. This study enrolled a total of 35 subjects, which limits the power to observe differences in key efficacy parameters such as PPPGA and PPPASI. Another limitation is that the duration of treatment was only 28 days. Future studies with RIST4721 should have an extended treatment duration to allow for a better understanding of the potential of RIST4721 as a chronic therapy for PPP, specifically as it pertains to the endpoints of PPPGA and PPPASI. Additional limitations of this study were related to the differences observed in the fresh pustule counts across investigative sites leading to a lack of a homogeneous study population. Future trials with RIST4721 should consider central review of images to better standardize the entry criteria and avoid enrolling patients that are improving significantly between screening and randomization.

Though the primary efficacy endpoints of relative change from baseline in fresh and total pustule counts at day 28 in RIST4721-201 did not demonstrate statistical significance, some secondary and exploratory endpoints numerically favored RIST4721, and the post hoc analyses demonstrated a potential for efficacy of RIST4721 in patients with PPP.

CONCLUSIONS

Once daily treatment with oral RIST4721 solution for 28 days was demonstrated to be well tolerated in subjects with moderate to severe PPP. While there were no differences in the primary efficacy parameters between the RIST4721 and placebo groups, post hoc subgroup analyses in subjects with progressing disease suggest there may be efficacy with RIST4721.

Preliminary data suggest RIST4721 is well tolerated and may be a potential therapy for patients with PPP. Further clinical trials with a longer treatment duration are needed to confirm these findings.

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Compliance with Ethics Guidelines. This study was approved by the Ethics Committees and Institutional Review Boards of participating centers in Canada (12 sites) and Germany (5 sites). The central Institutional Review Board in Canada was Advarra, and the central Ethics Committee at the coordinating center in Germany was Ethik-Kommission bei der Ärztekammer Niedersachsen (refer to the supplementary material [S3] for the full list of Institutional Review Boards and Ethics Committees consulted during the study). The study was conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines. Written informed consent was obtained from all individual participants included in the study.

Data Availability. Results from Study RIST4721-201 have been posted to the European Union Clinical Trials Register at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-004176-35/results.

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