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ORIGINAL ARTICLE

Oral orismilast: Efficacy and safety in moderate-to-severe psoriasis and development of modified release tablets

Richard B. Warren[1] | **Bruce Strober**[2] | **Jonathan I. Silverberg**[3] | **Emma Guttman**[4] | **Philippe Andres**[5] | **Jakob Felding**[5] | **Deniz Tutkunkardas**[5] | **Kim Kjøller**[5] | **Morten O. A. Sommer**[5,6] | **Lars E. French**[7,8]

[1]Dermatology Centre, Salford Royal NHS Foundation Trust, Manchester NIHR Biomedical Research Centre, The University of Manchester, Manchester, UK

[2]Yale University and Central Connecticut Dermatology, Connecticut, New Haven, USA

[3]George Washington University School of Medicine and Health Sciences, Washington, District of Columbia, USA

[4]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[5]UNION therapeutics A/S, Hellerup, Denmark

[6]Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark, Kongens Lyngby, Denmark

[7]Department of Dermatology and Allergy, University Hospital, Ludwig Maximilian University (LMU) Munich, Munich, Germany

[8]Dr. Philip Frost, Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, Florida, USA

Correspondence
Lars E. French, Klinik und Poliklinik für Dermatologie und Allergologie, Klinikum der Universität München, Frauenlobstr. 9-11, D-80337 Munich, Germany.
Email: lars.french@med.uni-muenchen.de

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Abstract

Background: Orismilast is a high-potency phosphodiesterase 4 (PDE4) inhibitor with enhanced selectivity for the PDE4B and PDE4D subtypes.

Objectives: The objective of this phase 2a trial was to examine the efficacy and safety of orismilast for psoriasis using a first-generation immediate-release (IR) formulation. The objective of the subsequent phase 1 trial was to test new formulations designed to minimize the gastrointestinal (GI)-related adverse events (AEs) observed with the first-generation IR formulation. We examined the following: (1) pharmacokinetic (PK) properties of orismilast modified release (MR) and IR, (2) food effects on PK properties of orismilast MR or IR, (3) safety of orismilast MR compared to placebo.

Methods: In a phase 2a prospective, randomized, double-blind, placebo-controlled trial, patients with moderate-to-severe psoriasis were randomized to receive 30 mg oral orismilast IR or placebo over 16 weeks. The single-site phase 1 trial consisted of three parts: (1) participants received a single 30 mg dose of orismilast MR and IR (open-label), (2) participants received 30 mg orismilast MR or IR under either fasting condition, following a high-fat meal or low-fat meal (open-label) and (3) participants received up to 60 mg orismilast MR twice-daily or a placebo for 17 days (double-blind).

Results: In the phase 2a trial, treatment with orismilast IR significantly improved the mean Psoriasis Area Severity Index score at week 16 compared to placebo. The phase 1 trial revealed comparable PK properties of the orismilast MR and IR formulations, with participants in the orismilast MR group experiencing fewer GI-related AEs than those receiving orismilast IR (16.7% vs. 33.3%).

Conclusion: Orismilast IR displayed higher efficacy compared to placebo in patients with moderate-to-severe psoriasis at week 16. Orismilast MR had similar PK properties and fewer GI disorders compared to the IR formulation in healthy participants. Future development of orismilast will be based on the MR formulation.

BACKGROUND

Psoriasis is a chronic, inflammatory skin disease characterized by well-demarcated, erythematous, scaly plaques. The most common type, psoriasis vulgaris (plaque psoriasis [psoriasis]), represents 80%–90% of psoriasis cases.[1] The pathogenesis of psoriasis is underpinned by activation of the T-helper 17 (Th17) pathway, but many inflammatory

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cytokines, including interleukin (IL)-17A, IL-17F, IL-22, IL-23 and tumour necrosis factor-alpha (TNF-α), play a role.[2,3] Despite advances in topical treatments and injectable biologics, an unmet need persists for long-term oral treatment that is efficacious, safe and convenient to use.

Phosphodiesterase 4 (PDE4) is an enzyme that regulates cyclic adenosine monophosphate (cAMP) signalling, which regulates inflammatory pathways. PDE4 enzymes consist of four subtypes: PDE4A–PDE4D and over 20 splice isoforms. The subtypes PDE4B and PDE4D modulate a broad spectrum of inflammatory signalling cascades,[4] whereas PDE4C is largely absent in most inflammatory cells.[4] PDE4 inhibition downregulates proinflammatory cytokines including TNF-α, interferon (IFN)-gamma, IL-4, IL5, IL-6, IL-8, IL-13, IL-17, IL-22 and IL-23.[5–7] Oral PDE4 inhibitors, including apremilast and roflumilast, are approved for the treatment of psoriasis and other chronic inflammatory diseases while crisaborole and difamilast have been launched for topical treatment of atopic dermatitis, and inhaled tanimilast is in phase 3 for treatment of COPD.[8–10] Hence, PDE4 inhibition is an established therapeutic target for chronic inflammatory diseases. Still, further development of improved oral PDE4 inhibitors is required to improve the efficacy and tolerability of oral PDE4 inhibitors, which are associated with nausea, diarrhoea and headache.

Orismilast is a high-potency PDE4 inhibitor that inhibits PDE4 subtypes associated with inflammation.[11,12] Orismilast demonstrated high selectivity for PDE4B and PDE4D subtypes in vitro, T-helper cell-related cytokine inhibition in human whole blood and human peripheral blood mononuclear cells and anti-inflammatory effects in a murine chronic oxazolone model (submitted for publication). Here, we report results from a phase 2a trial examining the efficacy and safety of oral orismilast immediate-release (IR) formulation in adults with moderate-to-severe psoriasis. Based on the adverse event (AE) profile observed in the phase 2a trial, a formulation study aimed to reduce the AEs was conducted in healthy volunteers. A key element in the healthy volunteer study was to explore a modified release (MR) oral formulation. The MR formulation was designed to lower the local gastric concentration of orismilast while maintaining the systemic pharmacokinetic (PK) observed with the IR formulation.

MATERIALS AND METHODS

Clinical studies were conducted in accordance with the principles issued by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), Declaration of Helsinki, and with the approval of national independent ethics committees.

Phase 2a trial: Proof of concept study design

The phase 2a trial was a single-centre (Charité University, Berlin, Germany), prospective, randomized, double-blind, two-arm, placebo-controlled study in adult patients with moderate-to-severe plaque psoriasis (Registered at ClinicalTrials.gov, NCT02888236 and EudraCT.ema.europa.eu, 2015-005279-25). In total, 36 patients were randomized (1:1) to receive treatment with 30 mg oral orismilast IR tablet or placebo, twice-daily for 16 weeks. The duration of the study was 23 weeks and included the following: (1) a screening period with two screening visits for eligibility and baseline assessments performed within 35 days before randomization; (2) a treatment period including a 1-week dose-escalation, followed by 15 weeks of treatment twice-daily with the full 30 mg orismilast IR or placebo; and (3) a follow-up visit, 14 days (±2) days after the last trial visit.

Phase 2a trial: Patient population

Patients between the age of 18–65 years with a clinical diagnosis of psoriasis, with or without psoriatic arthritis, for ≥6 months prior to the second screening visit were included. Moderate-to-severe psoriasis was determined by a Psoriasis Areaand Severity Index (PASI) score >10, covering >10% of body surface area (BSA), and a Physician's Global Assessment (PGA) with a disease severity score ≥3. Key exclusion criteria included previous exposure to apremilast, and therapy-resistant psoriasis defined as ≥2 treatment failures due to inadequate efficacy within the past 5 years to oral-systemic therapies, biologics, or ultraviolet light therapy.

Phase 2a trial: Objectives and outcomes

The primary objective was to evaluate the efficacy of 30 mg orismilast IR. The primary outcome was the PASI score at week 16. The secondary objectives were (1) to examine the effect of orismilast IR on psoriasis symptoms, (2) to investigate the effect of orismilast IR on itch intensity and (3) to investigate the safety and tolerability of orismilast IR compared to placebo. The secondary outcomes included treatment success defined as clear or almost clear according to PGA and itch numeric rating scale (NRS) at week 16. Exploratory endpoints included assessments of disease severity measured by ≥75% reduction from the baseline PASI (PASI-75), improvement in PGA and the dermatology life quality index (DLQI) at week 16. AEs and serious AEs (SAEs) were monitored throughout the trial to examine the safety and tolerability of orismilast IR.

Phase 2a trial: Statistical analysis

A total sample size of 36 was calculated based on the assumption that there would be a 7-point difference in the mean PASI score at week 16 between the orismilast and placebo group, with a 2-sided significance level of 5% to allow 80% statistical power. All significance tests were 2-sided and performed at the 5% significance level. Estimated treatment differences and 95% confidence intervals (CI) were calculated together with the

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corresponding *p*-value. Descriptive statistics for all endpoints were presented by treatment and week, as applicable.

The primary analysis included all randomized patients. PASI score at week 16 between orismilast and placebo was analysed using analysis of covariance (ANCOVA) model with treatment and site as factors, and baseline PASI as a covariate. PGA treatment success, PASI-75 and DLQI at week 16 were analysed using logistic regression and adjusted for site. Missing data were imputed using the last observation carried forward (LOCF). Safety analysis was conducted on all patients who received at least one dose of trial treatment, and AEs were presented using descriptive statistics.

Phase 1 trial: Study design

The phase 1 trial was a single-site, oral dose trial that examined the safety, tolerability and PK of orismilast MR and IR formulations (Registered at ClinicalTrials.gov, NCT03812198 and European Union Clinical Trials Register, 2018-003282-34). Healthy participants aged 18–65 years were included in the trial. Key exclusion criteria included prior treatment with orismilast and systemic or topical treatment within 14 days prior to the first dose administration.

The trial consisted of three parts. The open-label parts 1 and 2 examined multiple orismilast formulations however, only the results of the MR tablet and IR capsule are described here, for comparison purposes. In part 1, the PK of single-dose orismilast MR and IR was tested. Participants (n = 18) were randomized for treatment sequence to receive three different 30 mg orismilast formulations under fasting condition. PK properties of orismilast MR and IR are described here. Part 2 examined the effect of food on single-dose 30 mg orismilast PK testing the effect of fasting, low-fat meal and high-fat meal on the PK of orismilast MR and IR, respectively. Participants were randomized (1:1:1) to a treatment sequence and received 30 mg orismilast during fasting, low-fat meal and high-fat meal (n = 9). The food effects on orismilast MR PK are described here.

The double-blinded part 3 examined the PK, GI-related safety and tolerability of up-titrated 60 mg twice-daily orismilast MR after multiple dosing compared to placebo. Participants were randomized (3:1) to receive orismilast MR (n = 9) or placebo (n = 3). Orismilast MR was administered twice-daily for a total of 17 days. Orismilast MR was initiated at 10 mg twice-daily on days 1–2, increased to 20 mg twice-daily on days 3–4, to 30 mg twice-daily on days 5–6, to 40 mg twice-daily on days 7–8, to 50 mg twice-daily on days 9–10 and finally to 60 mg twice-daily on days 11–17 (morning dose only on day 17). PK parameters were calculated on day 1 and 17.

Phase 1 trial: Statistical analysis

Pharmacokinetic parameters were calculated using concentration data collected from pre-dose to 48 h post-dose in part 1 and from pre-dose to 72 h post-dose in part 2 of the phase 1 trial. PK parameters, including logarithmic values of $AUC_{0-\infty}$, AUC_{0-t}, C_{max}, $t_{1/2}$, and t_{max}, were measured for each formulation using a linear normal mixed model including fixed effects of formulation, period and a random effect of a person for part 1 and fixed effects of food regimen, period, and a random effect of a person for part 2. In part 3,

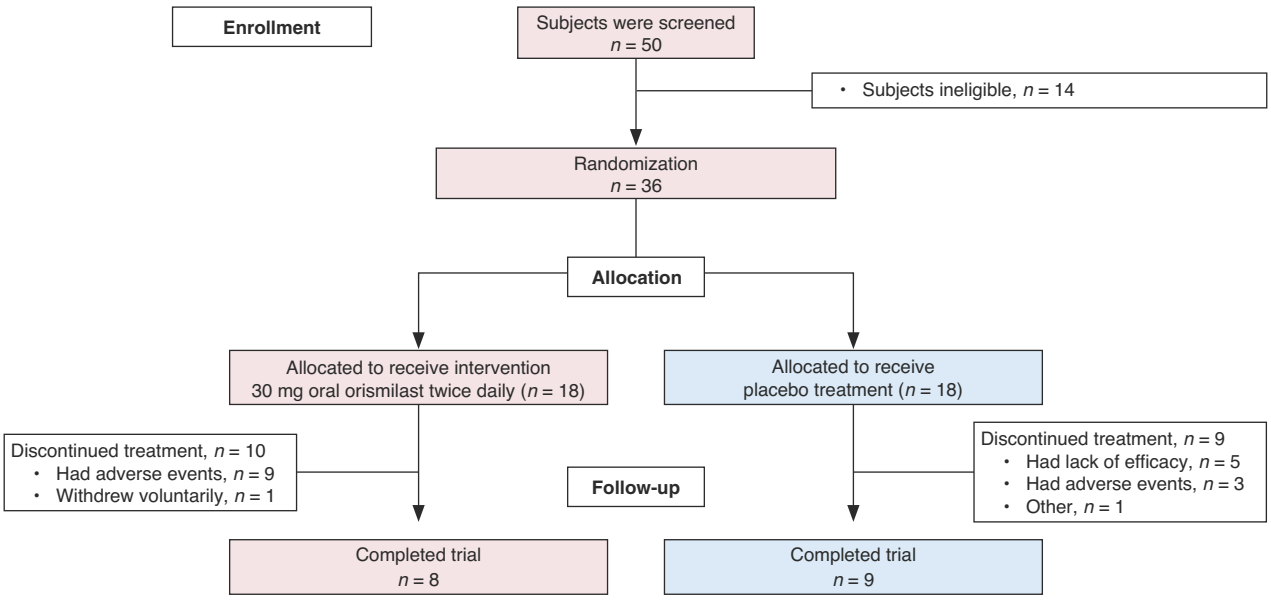

FIGURE 1 Phase 2a trial – patient enrolment, randomization and treatment.

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TABLE 1 Phase 2a trial – patient demographics and baseline characteristics

	Total (n = 36)	30 mg Orismilast IR (n = 18)	Placebo (n = 18)
Age (18–64 years old)			
Mean ± SD	44.0 ± 11.9	41.4 ± 12.4	46.6 ± 11.2
Median (range)	46.5 (20, 61)	43.0 (20, 61)	51.0 (22, 59)
Weight (kg)			
Mean ± SD	89.9 ± 17.2	91.0 ± 15.8	88.7 ± 18.8
Median (range)	90.0 (58.8, 126.4)	93.0 (58.8, 118.2)	85.0 (59.5, 126.4)
BMI (kg/m^2)			
Mean ± SD	28.2 ± 4.9	28.1 ± 4.6	28.3 ± 5.4
Median (range)	28.2 (19.6, 39.9)	28.1 (19.6, 37.3)	28.3 (20.8, 39.9)
Sex			
Male (n [%])	33 (91.7)	17 (94.4)	16 (88.9)
Female (n [%])	3 (8.3)	1 (5.6)	2 (11.1)
Race			
Caucasian (n [%])	35 (97.2)	17 (94.4)	18 (100.0)
Other (n [%])	1 (2.8)	1 (5.6)	0 (0.0)
Total (n [%])	36 (100.0)	18 (100.0)	18 (100.0)
Ethnicity			
Hispanic or Latino (n [%])	1 (2.8)	1 (5.6)	0 (0.0)
Other (n [%])	35 (97.2)	17 (94.4)	18 (100.0)
Total (n [%])	36 (100.0)	18 (100.0)	18 (100.0)
Fitzpatrick skin classification			
II (n [%])	19 (52.8)	9 (50.0)	10 (55.6)
III (n [%])	12 (33.3)	5 (27.8)	7 (38.9)
IV (n [%])	5 (13.9)	4 (22.2)	1 (5.6)
Total (n [%])	36 (100.0)	18 (100.0)	18 (100.0)
Baseline disease characteristics			
Duration of psoriasis (years)			
Mean ± SD	17.0 ± 12.1	17.0 ± 12.8	17.0 ± 11.6
Median (range)	14.0 (3, 47)	13.0 (3, 42)	15.0 (3, 47)
Total PASI score			
Mean ± SD	14.9 ± 3.4	14.9 ± 3.0	14.9 ± 3.9
Median (range)	14.5 (10.2, 23.0)	14.8 (11.4, 22.5)	14.3 (10.2, 23.0)
Total BSA (%)			
Mean ± SD	15.7 ± 5.9	15.8 ± 4.5	15.5 ± 7.1
Median (range)	14.0 (10.0, 35.5)	15.0 (10.0, 24.5)	12.8 (10.5, 35.5)
Physician's global assessment			
Moderate (n [%])	31 (86.1)	15 (83.3)	16 (88.9)
Severe (n [%])	5 (13.9)	3 (16.7)	2 (11.1)
Subject's global assessment			
Moderate (n [%])	26 (72.2)	14 (77.8)	12 (66.7)
Severe (n [%])	10 (27.8)	4 (22.2)	6 (33.3)

Abbreviations: BSA, body surface area; IR, immediate-release; PASI, Psoriasis Area Severity Index.

logarithmic values of $AUC_{0-\infty}$, AUC_{0-t}, C_{max}, $t_{1/2}$ and t_{max} were generated by group, treatment, and day. Safety analysis was conducted in each part of the phase 1 trial and included all participants who received orismilast in part 1–3 and placebo treatment in part 3. Descriptive statistics were used to present the plasma concentration, PK parameters, and safety

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TABLE 2 Summary of efficacy results of 30 mg orismilast IR twice-daily compared to placebo treatment at week 16 (n = 36)

Assessment endpoints	30 mg Orismilast IR (n = 18)	Placebo (n = 18)	Treatment difference or odds ratio (95% CI)	p-Value
Primary endpoint				
PASI score – LS means (95% CI)	7.1 (4.3 to 9.9)	13.1 (10.3 to 15.9)	−6.0 (−10.0 to −2.0)	0.005
Secondary endpoints				
PGA treatment success – number (%)	7/18 (38.9)	1/17 (5.6)	12.3 (1.7 to 256.1)	0.032
Itch NRS – LS means (95% CI)	3.4 (1.8 to 5.1)	5.7 (4.1 to 7.3)	−2.3 (−4.6 to 0.0)	0.053
Exploratory endpoints				
PASI-75 – number (%)	8/18 (44.4)	1/18 (5.6)	15.7 (2.2 to 333.5)	0.019
Improving ≥2 levels in PGA – number (%)	7/18 (38.9)	1/18 (5.6)	12.3 (1.7 to 256.1)	0.032
DLQI score – LS means (95% CI)	3.8 (−0.4 to 8.1)	12.9 (8.5 to 17.2)	−9.1 (−15.4 to −2.8)	0.008

Note: The values reported for LS means are treatment differences and the values for numbers (%) are odds ratios.

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; IR, immediate release; LS means, least-squares means; NRS, numeric rating scale; PASI, Psoriasis Area and Severity Index; PGA, Physician's global assessment.

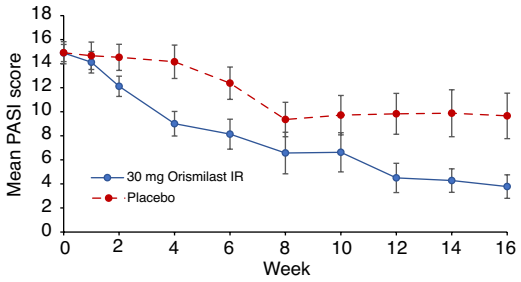

FIGURE 2 Mean PASI score change over a 16-week treatment period in patients with moderate-to-severe psoriasis treated with 30 mg orismilast IR twice-daily (n = 18) and placebo (n = 18). The mean PASI score decreased from 14.9 at baseline to 7.0 and 13.2 based on LOCF in the orismilast IR and placebo group, respectively. Data are mean ± SEM. IR, immediate release; LOCF, last observation carried forward; PASI, Psoriasis Area and Severity Index; SEM, standard error of mean.

data. Since orismilast MR was chosen for further clinical development, the results that belong to orismilast MR and orismilast IR, for comparison purposes, are depicted in this manuscript.

RESULTS

Phase 2a trial: Patient population

In total, 36 patients were randomized (1:1) to receive orismilast IR or placebo for 16 weeks. Overall, 55.6% of patients from the orismilast IR group and 50.0% of patients from the placebo group discontinued the trial primarily due to GI-related AEs and lack of efficacy, respectively (Figure 1). No patients missed any visits prior to withdrawal or the end of the trial. A detailed summary of demographics and baseline characteristics is presented in Table 1. Demographic data did not show major differences between the two treatment groups.

Efficacy of orismilast IR in patients with moderate-to-severe psoriasis

Treatment with 30 mg orismilast resulted in significant improvement of the mean PASI score at week 16 based on analysis using ANCOVA with LOCF as compared to placebo, with a least-squares (LS) mean difference of −6.0 (7.1 vs. 13.1; p = 0.005) (Table 2). A rapid reduction in the mean PASI score was noted in the orismilast group during the initial 4 weeks of treatment, with an observed mean PASI score of 3.8 and 9.7 in the orismilast and placebo group at week 16, respectively (Figure 2).

Patients in the orismilast group were more likely to achieve PASI-75 at week 16 compared to placebo. The proportion of patients on orismilast achieving PASI-75 at week 16 was 44.4% compared to 5.6% for patients on placebo (odds ratio [OR]: 15.7, p = 0.019). At week 16, more patients in the orismilast IR group also achieved treatment success according to PGA and improved ≥2 levels on the PGA scale compared to placebo (OR: 12.3, p = 0.032) and (OR: 12.3, p = 0.032), respectively. Patients in the orismilast IR group reported significant improvements in their quality of life compared to the placebo group at week 16, with a treatment difference of −9.1 in DLQI score (3.8 vs. 12.9; p = 0.008). Furthermore, the observed mean itch scores decreased from baseline to week 6, from 6.4 to 3.0 in the orismilast IR group and from 6.3 to 4.7 in the placebo group (Table S4). The observed scores at visits after Week 6 should be interpreted with caution, as the number of subjects with an assessment of this endpoint at these visits was low ($n \leq 7$ in the orismilast IR group and $n \leq 4$ in the placebo group).

Safety of orismilast in patients with moderate-to-severe psoriasis

The number of patients that reported any AE was similar between orismilast and placebo (Table 3). Two patients in the

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TABLE 3 Summary of adverse events reported during the treatment period

	30 mg Orismilast IR (*N* = 18), *n* (%)	Placebo (*N* = 18), *n* (%)
Any adverse event	17 (94.4)	16 (88.9)
Gastrointestinal-related AEs	16 (88.9)	5 (27.8)
AE leading to withdrawal	9 (50.0)	3 (16.7)
Serious AEs	2 (11.1)	1 (5.6)
Severe AEs	1 (5.6)	2 (11.1)
Frequent treatment-emergent adverse events by SOC and preferred terms		
Gastrointestinal disorders		
Nausea	11 (61.1)	1 (5.6)
Diarrhoea	9 (50.0)	0 (0.0)
Vomiting	3 (16.7)	1 (5.6)
Abdominal pain	3 (16.7)	1 (5.6)
Flatulence	2 (11.1)	1 (5.6)
Toothache	1 (5.6)	1 (5.6)
Dyspepsia	1 (5.6)	1 (5.6)
SOC total	16 (88.9)	3 (16.7)
Infections and infestations total		
Nasopharyngitis	5 (27.8)	5 (27.8)
Gastroenteritis	1 (5.6)	1 (5.6)
SOC total	6 (33.3)	6 (33.3)
Nervous system disorders total		
Headache	5 (27.8)	2 (11.1)
Dizziness	4 (22.2)	0 (0.0)
SOC total	1 (5.6)	2 (11.1)
Musculoskeletal and connective tissue disorder		
Back pain	2 (11.1)	2 (11.1)
Muscle spasms	1 (5.6)	1 (5.6)
SOC total	3 (16.7)	3 (16.7)
General disorders and administration site conditions		
Fatigue	2 (11.1)	0 (0.0)
Pain	1 (5.6)	1 (5.6)
SOC total	3 (16.7)	1 (5.6)
Psychiatric disorders		
Insomnia	2 (11.1)	2 (11.1)
Thinking abnormal	2 (11.1)	0 (0.0)
SOC total	2 (11.1)	2 (11.1)
Skin and subcutaneous tissue disorders		
Hyperhidrosis	2 (11.1)	1 (5.6)
SOC total	2 (11.1)	1 (5.6)
Metabolism and nutrition disorders		
Decreased appetite	2 (11.1)	0 (0.0)
SOC total	2 (11.1)	0 (0.0)
Renal and urinary disorders		
Glycosuria	2 (11.1)	0 (0.0)
SOC total	2 (11.1)	0 (0.0)
Blood and lymphatic system disorders		
Lymphopenia	1 (5.6)	1 (5.6)
SOC total	1 (5.6)	1 (5.6)

Abbreviations: AE, adverse events; IR, immediate release; *n*, number of observations; *N*, number of participants; SOC, system organ class.

placebo group and one patient in the orismilast group reported an SAE. No deaths occurred during the trial period.

Gastrointestinal-related AEs and infections and infestations were the most common AEs in the orismilast IR group (88.9%) and the placebo group (33.3%), respectively. In the orismilast group, nausea (61.1%) and diarrhoea (50.0%) were the most reported AEs. More patients in the orismilast group discontinued the trial due to AEs compared to the placebo group (50.0% vs. 16.7%).

Phase 1 trial: Pharmacokinetics, safety, and tolerability of orismilast MR formulation

Due to the high rates of GI-related AEs and associated discontinuation rates in the phase 2a trial, multiple orismilast formulations were developed to modify the release profile by reducing the local gastric concentration of orismilast to improve GI tolerance while maintaining the systemic PK observed with the IR formulation.

The results of part 1 of the phase 1 trial show that orismilast MR achieved comparable PK properties to orismilast IR (Table 4). The maximum plasma concentration (C_{max}) of the MR and IR formulation was 96.9 and 109 ng/ml, respectively. Despite the slower release profile of the MR formulation, the time to C_{max} was similar for both formulations; 2.37 h for MR and 2.41 h for IR. The systemic exposure ($AUC_{0-\infty}$) to orismilast MR and IR was 500 and 512 ng h/ml, respectively. Orismilast MR and IR displayed a similar half-life of 6.67 and 6.48 h, respectively.

The most common AEs in part 1 were GI and nervous system disorders (Table 5). All GI-related AEs were mild. Fewer participants in the MR formulation group (16.7%) reported GI disorders compared to the IR formulation group (33.3%). Notably, the MR formulation did not evoke any incidents of nausea. Conversely, nausea was among the most reported AE in orismilast IR group (27.8%). Nervous system disorders were more prevalent in participants treated with the MR formulation (33.3%) compared to the IR formulation (22.2%).

In part 2, nine participants were randomized (1:1:1) to receive orismilast under fasting conditions, with a low-fat meal, or with a high-fat meal. Administering orismilast MR with a low-fat meal resulted in comparable exposure to fasting ($AUC_{0-\infty}$ 529 ng h/ml vs. 507 ng h/ml), whereas administering with a high-fat meal was associated with an increased exposure compared to fasting ($AUC_{0-\infty}$ 748 ng h/ml vs.

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507 ng h/ml) (Table 6). The safety results of oral orismilast under fasting conditions are summarized in Table S6.

In part 3, 12 participants were randomized to up-titration to 60 mg orismilast MR twice-daily ($n = 9$) or placebo ($n = 3$), under fasting conditions. The PK parameters on day 1 (10 mg single-dose) and day 17 (multiple-dose 60 mg twice-daily) are described in Table S7.

Most AEs in the orismilast MR group were mild (~93%) and 7 were of moderate severity (~7%) (Table S8). The most frequently reported GI-related AE was nausea (11 events), followed by diarrhoea (6 events) (Table 7). Nausea was dose-dependent with five episodes being observed on doses 10–50 mg twice-daily, and six episodes at 60 mg twice-daily. All GI-related AEs were mild, except for one moderate severity event of nausea.

TABLE 4 Summary of PK parameters of single-dose orismilast MR compared to orismilast IR

Parameter	30 mg Orismilast IR ($N = 18$)	30 mg Orismilast MR ($N = 18$) (ratio vs. IR and 99.375% CI)
AUC_{0-t} (ng h/ml)	502	482 (0.96 [0.76, 1.21])
$AUC_{0-\infty}$ (ng h/ml)	512	500 (0.98 [0.73, 1.30])
C_{max} (ng/ml)	109	96.9 (0.89 [0.68, 1.18])
t_{max} (h)[a]	2.37	2.41 (0.98 [0.64, 1.50])
$t_{1/2}$ (h)	6.67	6.48

Note: Geometric mean (CV%) [*n*] data are presented.

Abbreviations: $AUC_{0-infinity}$, area under the concentration-time curve from time 0 to infinity; AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; CI, confidence interval; C_{max}, maximum observed plasma concentration; IR, immediate release; MR, modified release; *N*, number of participants; PK, pharmacokinetic; $t_{1/2}$, apparent plasma terminal elimination half-life; t_{max}, time of the maximum observed plasma concentration.

[a]Median (min–max) [*n*].

TABLE 5 Frequent treatment-emergent adverse events of single-dose orismilast MR compared to orismilast IR

System organ class	30 mg Orismilast MR ($N = 18$), *n* (%)	30 mg Orismilast IR ($N = 18$), *n* (%)
Gastrointestinal disorders	3 (16.7)	6 (33.3)
Nausea	0 (0.0)	5 (27.8)
Diarrhoea	2 (11.1)	2 (11.1)
Abdominal pain	0 (0.0)	1 (5.6)
Constipation	1 (5.6)	0 (0.0)
Nervous system disorders	6 (33.3)	4 (22.2)
Headache	4 (22.2)	2 (11.1)
Dizziness	3 (16.7)	3 (16.7)
Presyncope	1 (5.6)	0 (0.0)

Abbreviations: IR, immediate release; MR, modified release; *n*, number of observations; *N*, number of participants.

DISCUSSION

The phase 2a trial provides a proof of concept on the efficacy of oral orismilast IR in patients with moderate-to-severe psoriasis. Administration with 30 mg orismilast IR resulted in significant improvements in PASI score (primary endpoint) and PGA treatment success at week 16, compared to placebo (7.1 vs. 13.1; $p = 0.005$ and 38.9% vs. 5.6%; $p = 0.032$, respectively) (Table 2). Psoriasis can reduce patients' quality of life, leading to psychological stress, avoidance of social environments and an increased risk of mood disorders.[13–15] Results from the phase 2a trial showed a statistically significant and clinically relevant improvement[16] in the quality of life of patients treated with oral orismilast compared to the placebo group, with a placebo-subtracted 9.1-point improvement (3.8 vs. 12.9; $p = 0.008$) (Table 2).

The only oral PDE4 inhibitor licensed in the treatment of moderate-to-severe psoriasis is apremilast. In the ESTEEM-1 and ESTEEM-2 phase 3 studies, apremilast showed a PASI-75 of 33.1% vs. 5.3% (placebo) and 28.8% vs. 5.8% (placebo), respectively using a LOCF analysis.[17,18] The percentage of patients achieving PGA success with apremilast was 21.7% vs. 3.9% (placebo) and 20.4% vs. 4.4% (placebo) in ESTEEM-1 and ESTEEM-2, respectively. Moreover, the placebo-subtracted DLQI improvements were 4.5 points in ESTEEM-1 and 3.9 points in ESTEEM-2.[17,18] Compared with the ESTEEM-1 and ESTEEM-2 results, the orismilast phase 2a trial shows the potential for improved efficacy and patient-reported outcomes profile.

In addition to being efficacious, it is necessary to ensure oral medications developed for psoriasis management are safe and tolerable. Although no significant safety concerns

TABLE 6 The effect of food on PK parameters of single-dose 30 mg orismilast MR

Parameter	Fasting ($N = 9$)	Low-fat meal ($N = 9$) (ratio vs. fasted and 99.375% CI)	High-fat meal ($N = 9$) (ratio vs. fasted and 99.375% CI)
AUC_{0-t} (ng h/ml)	480	531 (1.11 [0.90, 1.37])	731 (1.52 [1.23, 1.88])
$AUC_{0-\infty}$ (ng h/ml)	507	529 (1.04 [0.83, 1.32])	748 (1.48 [1.17, 1.86])
C_{max} (ng/ml)	101	88.7 (0.88 [0.62, 1.25])	116 (1.15 [0.81, 1.63])
t_{max} (h)	2.74	4.11 (1.50 [0.73, 3.05])	4.16 (1.52 [0.74, 3.09])

Abbreviations: $AUC_{0-infinity}$, area under the concentration-time curve from time 0 to infinity; AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; CI, confidence interval; C_{max}, maximum observed plasma concentration; MR, modified release; *N*, number of participants; PK, pharmacokinetic; t_{max}, time of the maximum observed plasma concentration.

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TABLE 7 Distribution of GI-related AEs over the course of treatment with orismilast MR in healthy participants – phase 1 trial, part 3

Preferred term	10 mg BID, *n* (number of events)	20 mg BID, *n* (number of events)	30 mg BID, *n* (number of events)	40 mg BID, *n* (number of events)	50 mg BID, *n* (number of events)	60 mg BID, *n* (number of events)	Total, *n* (number of events)
Abdominal distension	1 (1)	–	–	–	–		1 (1)
Abdominal pain	1 (1)	1 (1)	–	–	–	–	1 (2)
Abdominal pain upper	–	–	1 (1)	–	–	–	1 (1)
Diarrhoea	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	5 (6)
Nausea	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	3 (6)	5 (11)
Odynophagia	–	–	–	–	–	1 (1)	1 (1)
Toothache	–	–	–	–	–	1 (1)	1 (1)
Vomiting	–	1 (1)	–	–	–	–	1 (1)
Total	1 (4)	2 (4)	2 (3)	1 (2)	2 (2)	4 (9)	6 (24)

Abbreviations: AE, adverse events; BID, twice-daily administration; GI, gastrointestinal; MR, modified release.

were reported in the phase 2a trial, there was a high level of intolerance due to GI-related AEs in the oral orismilast IR group, which led to half of the patients discontinuing the trial. A similar proportion of patients withdrew from the placebo group, due to a lack of efficacy. An oral formulation of orismilast with an improved tolerability profile could increase the retention times, thereby increasing the proportion of patients responding to treatment. Accordingly, a phase 1 trial was conducted, testing multiple orismilast formulations with altered release profiles, aiming to find a release profile that would reduce the GI-related AEs.

The phase 1 trial provides valuable insight into the tolerability profile of the orismilast MR formulation and paves the way for future clinical development of orismilast. There were no statistically significant differences in PK parameters between the MR and IR formulations, indicating comparable bioavailability between the two formulations. The comparable systemic bioavailability is expected to translate into comparable efficacy profiles of the two formulations. Importantly, treatment with the MR formulation demonstrated an improved safety profile and tolerability compared to the IR formulation, with the exception of a higher incidence of nervous-system-related AEs. Future dose-finding studies will be required to clarify if these findings are also observed in larger patient populations.

Notably, the MR formulation did not result in nausea in the phase 1 trial, while nausea was the most common AE in participants who received an IR formulation in both the phase 1 trial and phase 2a trial. Previous research implicates a central effect of PDE4 inhibitors, which leads to GI-related AEs.[19] The identical t_{max} values of the MR and IR formulations and comparable AUC and C_{max} combined with fewer GI-related AEs indicate that the central effect of PDE4 inhibitors may not be the only reason for GI-related AEs.

FUTURE CONSIDERATIONS

The findings from the present clinical trials indicate the potential of oral orismilast MR for the treatment of multiple chronic inflammatory conditions, where the regulation of upstream inflammatory pathways by a potent PDE4 inhibitor would be beneficial. Dermatological conditions including psoriasis, atopic dermatitis and hidradenitis suppurativa are the first therapeutic areas in which orismilast MR is being developed. Importantly, as chronic diseases require long-term treatment, comorbidities and concomitant conditions must be considered when selecting the most appropriate therapy for patients. In many cases, an oral PDE4 inhibitor could be an attractive therapy and benefits beyond disease control have been reported (e.g. weight loss[20] and reduced rate of cardiovascular events[21]), but under certain conditions (e.g. in pregnant patients) a cautious approach is needed.[22]

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Bruce Strober https://orcid.org/0000-0002-8394-2057
Jonathan I. Silverberg https://orcid.org/0000-0003-3686-7805
Emma Guttman https://orcid.org/0000-0002-9363-324X
Deniz Tutkunkardas https://orcid.org/0000-0002-9390-6105
Lars E. French https://orcid.org/0000-0002-4629-1486

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