ORIGINAL ARTICLE

Effects of oral roflumilast therapy on body weight and cardiometabolic parameters in patients with psoriasis – results from a randomized controlled trial (PSORRO)

Mette Gyldenløve, MD, PhD,[a,b] Jennifer Astrup Sørensen, MD,[c] Simon Fage, MD,[d] Howraman Meteran, PhD,[e,f] Lone Skov, DMSc,[a,b] Claus Zachariae, DMSc,[a,b] Filip Krag Knop, PhD,[b,g,h] Mia-Louise Nielsen, PhD,[c] and Alexander Egeberg, DMSc[b,c]

Background: Weight loss is reported with oral roflumilast, which is approved for chronic obstructive pulmonary disease (COPD). Recently, the drug has shown efficacy in psoriasis, a disease strongly linked to overweight/obesity.

Objective: To describe the effects of oral roflumilast on body weight and cardio-metabolic parameters in patients with psoriasis.

Methods: Posthoc analyses from the PSORRO study, where patients with moderate-to-severe plaque psoriasis were randomized 1:1 to oral roflumilast 500 μg once-daily or placebo for 12 weeks, followed by active, open-label treatment through week 24 in both groups. Changes in body weight, blood pressure, gastrointestinal symptoms, and laboratory tests were registered. No lifestyle or dietary interventions were applied.

Results: Forty-six patients were randomized. Baseline characteristics across groups were comparable; mean weight was 103.6 kg. In patients receiving roflumilast, median weight change was −2.6% and −4% at week 12 and 24, respectively. Corresponding numbers were 0.0% and 1.3% in patients initially allocated to placebo. Reduced appetite was more frequent with active therapy. No changes in blood pressure or laboratory tests were observed.

Limitations: Posthoc analyses and low numbers.

Conclusion: Oral roflumilast induced weight loss and reduced appetite, which support the growing evidence of roflumilast as an attractive treatment alternative for patients with psoriasis. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2024.02.036.)

From the Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark[a]; Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark[b]; Department of Dermatology, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark[c]; Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark[d]; Department of Medicine, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark[e]; Department of Public Health, University of Aarhus; Aarhus, Denmark[f]; Center for Clinical Metabolic Research, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark[g]; and Steno Diabetes Center Copenhagen, Herlev, Denmark.[h]

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Correspondence to: Mette Gyldenløve, MD, PhD, Associate Professor, Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Gentofte Hospitalsvej 15, Hellerup, 2900, Denmark. E-mail: mette.gyldenloeve@regionh.dk.

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INTRODUCTION

Psoriasis is a common inflammatory skin disease associated with a range of cardiometabolic comorbidities, including obesity.[1] In addition to the close link to leading causes of morbidity and mortality,[2] obesity also has implications for psoriasis management. Thus, obese patients with psoriasis respond less well to systemic psoriasis therapy,[3] and weight loss reduces psoriasis severity.[4,5]

Lifestyle interventions, that is, healthy diet and physical exercise, are recommended in weight management, but often fail to generate clinically meaningful and durable weight loss. At least partly, this is due to various antagonizing biological processes protecting against energy storage depletion. According to authoritative guidelines, pharmaceutical anti-obesity therapy should be considered in people with obesity (body mass index [BMI] > 30 kg/m^2) or overweight (BMI >27 kg/m^2) with one or more weight-related comorbidities.[6] Despite this, only a few percent of eligible patients are prescribed these drugs.[7]

Oral roflumilast is a phosphodiesterase (PDE)-4 inhibitor, which has been approved for the treatment of severe chronic obstructive pulmonary disease (COPD) for more than a decade. Generic versions were marketed in the United States in 2022. Recent evidence indicates that oral roflumilast holds a therapeutic potential in inflammatory skin conditions, including psoriasis.[8-11] Interestingly, weight loss is a frequently reported side effect to oral roflumilast therapy.[9,10,12,13]

The aim of this study was to assess the effects of oral roflumilast therapy on body weight and cardiometabolic parameters in patients with moderate-to-severe plaque psoriasis.

CAPSULE SUMMARY

- Recent evidence indicates that roflumilast holds a therapeutic potential in psoriasis; a chronic inflammatory disease linked to overweight/obesity. Weight loss is a frequently reported side effect to oral roflumilast.
- The current findings support oral roflumilast as an attractive treatment alternative for psoriasis, especially in overweight or obese patients.

METHODS

Study design

The present report comprises secondary endpoint data from the Psoriasis Treatment with Oral Roflumilast (PSORRO) study — an investigator-initiated, company-independent, multicenter, randomized, double-blind, placebo-controlled trial, conducted between January 1, 2021 and December 12, 2022 (EudraCT 2020-000711-76; ClinicalTrials.gov (NCT04549870)). The primary study outcome was a 75% or greater reduction from baseline in the psoriasis and severity index (PASI) at week 12, which was achieved by 35% of the patients receiving active therapy compared to 0% in the placebo group. Efficacy and safety results have previously been published, along with detailed protocol information.[8]

In short, eligible patients were ≥18 years, had a BMI ≥20 kg/m^2, and were diagnosed with stable, moderate-to-severe plaque psoriasis (PASI ≥8). Topical and systemic therapy for psoriasis were not accepted 2 and 4 weeks, respectively, before randomization or during the study period. At baseline, patients were randomized 1:1 to oral roflumilast 500 μg once daily (ie, the in-label marketed dose for COPD), or placebo. The treatment was blinded from week 0 to week 12. Thereafter, all patients received open-label treatment with oral roflumilast 500 μg once daily until week 24. No lifestyle interventions or dietary restrictions were included in the study design.

Assessments

Evaluated as changes from baseline to week 12 and 24, respectively, outcome measurements included the following: body weight in kg and percent, proportion of patients with a body weight reduction of ≥3%, ≥5%, ≥10%, or ≥15%, respectively, BMI, blood pressure, cholesterol levels, glycated hemoglobin A1c (HbA1c), high-sensitivity C-reactive protein (hsCRP), creatinine, and alanine transaminase (ALAT). In addition, changes in appetite and the presence of nausea, abdominal pain, or diarrhea during the study period was recorded.

Overall efficacy and safety assessments have previously been published.[8]

Abbreviations used:

AE:	adverse event
ALAT:	alanine transaminase
ANCOVA:	analysis of covariance
ASAT:	aspartate transaminase
BMI:	body mass index
COPD:	chronic obstructive pulmonary disease
EudraCT:	European Union drug regulating authorities clinical trials
GLP-1:	glucagon-like peptide 1
HbA1c:	glycated hemoglobin A1c
HDL:	high-density lipoprotein
hsCRP:	high-sensitivity C-reactive protein
IQR:	interquartile range
ITT:	intention to treat
LDL:	low-density lipoprotein cholesterol
LOCF:	last observation carried forward
mBOCF:	modified baseline observation carried forward
mNRI:	modified non-responder imputation
NRI:	non-responder imputation
NRS:	numeric rating scale
PASI:	psoriasis area and severity index
PDE-4:	phosphodiesterase-4
PSORRO:	Psoriasis Treatment with Oral Roflumilast (PSORRO)
SD:	standard deviation

Statistical analysis

Data analyses were performed using Python version 3.7.6, including relevant packages (Python Software Foundation). Categorical variables were presented as frequencies and percentages; continuous variables as means and standard deviations (SDs) (normally distributed data) or medians and interquartile ranges (IQR) (non-normally distributed data). Outcomes were evaluated based on intention to treat (ITT) and tested with Fisher's exact tests (binary outcomes) and Mann–Whitney U tests (numeric variables). Spearman's rank correlation test was used to quantify the association between changes in weight and PASI. Missing data were handled with nonresponder imputations (NRIs) for binary outcomes and last observation carried forward (LOCF) for numeric outcomes. *P*-values were adjusted for multiple testing using the Benjamini–Hochberg procedure with a false discovery rate of 0.05.

RESULTS

A total of 46 patients were enrolled in the trial, of which 42 and 38 patients completed week 12 and 24, respectively. Demographics and baseline characteristics were generally comparable in the 2 treatment groups (Table I). In the active treatment arm, mean body weight was 102.0 kg, BMI 33.3 kg/m^2, and mean waist circumference 106.8 cm; 13% of the participants had type 2 diabetes. In the placebo arm, mean body weight at randomization was 105.1 kg, BMI 32.2 kg/m^2, and mean waist circumference 109.0 cm; 9% of the participants were diagnosed with type 2 diabetes.

In the roflumilast group, weight loss was observed from week 4 to 24. The median weight change at week 12 was −2.6% (−2.3 kg) compared with 0% (0.0 kg) in the placebo group. The weight loss was moderately correlated with PASI change (coefficient 0.52, *P*-value .0004) and weakly/moderately correlated with baseline weight (coefficient −0,37, *P*-value .02) (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/w6p652wrb9/1). At week 24, median weight change in participants receiving roflumilast since baseline was −4.0% (−3.2 kg), while participants initially in the placebo group showed a 1.3% (1.3 kg) weight reduction from baseline. No significant correlation between weight loss and PASI change was demonstrated. During the 24-week study, a total of 57%, 30%, 17%, and 13% of patients treated with roflumilast since randomization lost ≥3%, ≥5%, ≥10%, and ≥15%, respectively, of their baseline body weight (Fig 1 and Table II). No patients became underweight (Supplementary Fig 2, available via Mendeley at https://data.mendeley.com/datasets/w6p652wrb9/1).

Reduced appetite was reported by more patients in the roflumilast group compared to placebo, however statistical significance was only seen at week 4 (61% vs 26%, *P*-value .02). At week 24, numbers were identical irrespective of the duration of active therapy in the 2 arms (35% vs 35%, *P*-value 1.0). In addition to reduced appetite, nausea, abdominal pain, and diarrhea generally appeared to be more prevalent the first weeks after therapy initiation and thereafter diminished (Supplementary Table I and Fig 3, available via Mendeley at https://data.mendeley.com/datasets/w6p652wrb9/1).

During the study period, no changes were observed in cholesterol levels, HbA1c, hsCRP, creatinine, or ALAT. Sub-analyses according to diabetes status (n = 3 and 2 in the roflumilast and placebo group, respectively) did not change the results. Notably, HbA1c remained unchanged after 12 weeks of roflumilast treatment demonstrating a median of 34.0 (33.0; 40.0) in participants with diabetes compared to 35.0 (33.0; 37.0) in nondiabetic participants (*P*-value .76, adjusted for multiple testing). No clinically significant changes were recorded in blood pressure or pulse during the 24 study weeks.

No patients underwent bariatric surgery or received body weight-lowering medications before or during the trial period.

DISCUSSION

In this randomized placebo-controlled trial in patients with psoriasis, we observed a median

Table I. Patient baseline characteristics

	Roflumilast *n* = 23	Placebo *n* = 23	All *n* = 46
Demographics			
Age, yr	38.0 (30.0; 43.0)	39.0 (32.5; 50.0)	38.5 (30.0; 46.2)
Men, *n*	15 (65)	19 (83)	34 (74)
Caucasian, *n*	23 (100)	23 (100)	46 (100)
Clinical presentation			
Weight, kg	102.0 (23.5)	105.1 (21.1)	103.6 (22.2)
Body mass index, kg/m^2	33.3 (6.6)	32.2 (5.9)	32.7 (6.2)
Waist circumference			
Mean, cm	106.8 (19.5)	109.0 (15.5)	107.9 (17.4)
Distribution			
>88, *n* females	7 (88)	3 (75)	10 (834)
>102, *n* males	10 (67)	14 (74)	24 (71)
Waist-hip ratio	0.9 (0.9; 1.0)	1.0 (0.9; 1.0)	1.0 (0.9; 1.0)
Systolic blood pressure, mmHg	137 (130; 155)	137 (128; 150)	137 (128; 153)
Diastolic blood pressure, mmHg	90 (13)	88 (14)	89 (13)
Pulse, beats/min	77 (14)	82 (13)	79 (14)
Coexisting conditions at screening			
Type-2 diabetes, *n*[*]	3 (13)	2 (9)	5 (11)
Prediabetes, *n*[†]	2 (9)	2 (9)	4 (9)
Dyslipidemia, *n*	4 (17)	1 (4)	5 (11)
Hypertension, *n*	6 (26)	4 (17)	10 (22)
Biochemistry			
HbA1c, mmol/mol	35 (34; 39)	35 (33; 37)	35 (33; 38)
Total cholesterol, mmol/L	4.7 (1.0)	4.7 (0.6)	4.7 (0.8)
HDL cholesterol, mmol/L	1.1 (0.3)	1.1 (0.2)	1.1 (0.2)
LDL cholesterol, mmol/L	2.8 (0.8)	2.9 (0.5)	2.8 (0.6)
Triglycerides, mmol/L	1.4 (1.2; 2.4)	1.6 (1.2; 2.2)	1.5 (1.2; 2.3)
Creatinine, μmol/L	73 (15)	72 (15)	72 (15)
ALAT, U/L	29 (20; 43)	35 (20; 50)	32 (20; 46)
Hs-CRP, mg/L	2.8 (2.5; 5.5)	2.8 (2.2; 4.5)	2.8 (2.4; 5.0)

Data are shown for all randomized patients. Categorical variables are presented in frequencies and percentages. Numerical data are shown in mean and SD (normally distributed data) or median and IQR (non-normally distributed data).
ALAT, Alanine transaminase; *BMI*, body mass index; *HbA1c*; glycated hemoglobin A1c; *HDL*, high-density lipoprotein; *hs-CRP*, high-sensitivity C-reactive protein; *IQR*, interquartile range; *LDL*, low-density lipoprotein; *SD*, standard deviation.
[*]Type 2 diabetes defined as HbA1c ≥ 48 mmol/mol or antidiabetic medication at screening.
[†]Prediabetes defined as HbA1c 42-47 mmol/mol.

body weight reduction of 4% (3.2 kg) with 24 weeks of oral roflumilast monotherapy and no lifestyle interventions. After 12 weeks, a total of 35% of patients treated with roflumilast had lost 5% or more of their baseline bodyweight, which is widely accepted as a clinically meaningful change,[14] compared with 0% in the placebo group. No patients became underweight during the study.

According to the summary of product characteristics, oral roflumilast therapy is frequently accompanied by weight loss.[12] It appears to be independent of potentially co-occurring gastrointestinal side effects, for example diarrhea, although patients reporting such symptoms may experience even greater weight losses.[15] The mode of action is sparsely investigated, but some evidence point towards increased energy expenditure[16] or glucagon-like peptide 1 (GLP-1)-mediated mechanisms,[17-20] the latter supported by the observations of reduced appetite in the current trial. Thus, GLP-1, an incretin hormone secreted from enteroendocrine cells in response to food intake, plays an important role in satiety regulation,[21] and GLP-1 analogs represent an established treatment option for obesity. In the current trial, gastrointestinal symptoms, that is, nausea, abdominal pain, and/or diarrhea, were reported in up to 39% of patients during the first 4 weeks after initiation of oral roflumilast, but thereafter diminished. These findings support that the weight loss accompanying oral roflumilast therapy is driven by other factors than gastrointestinal side effects only.

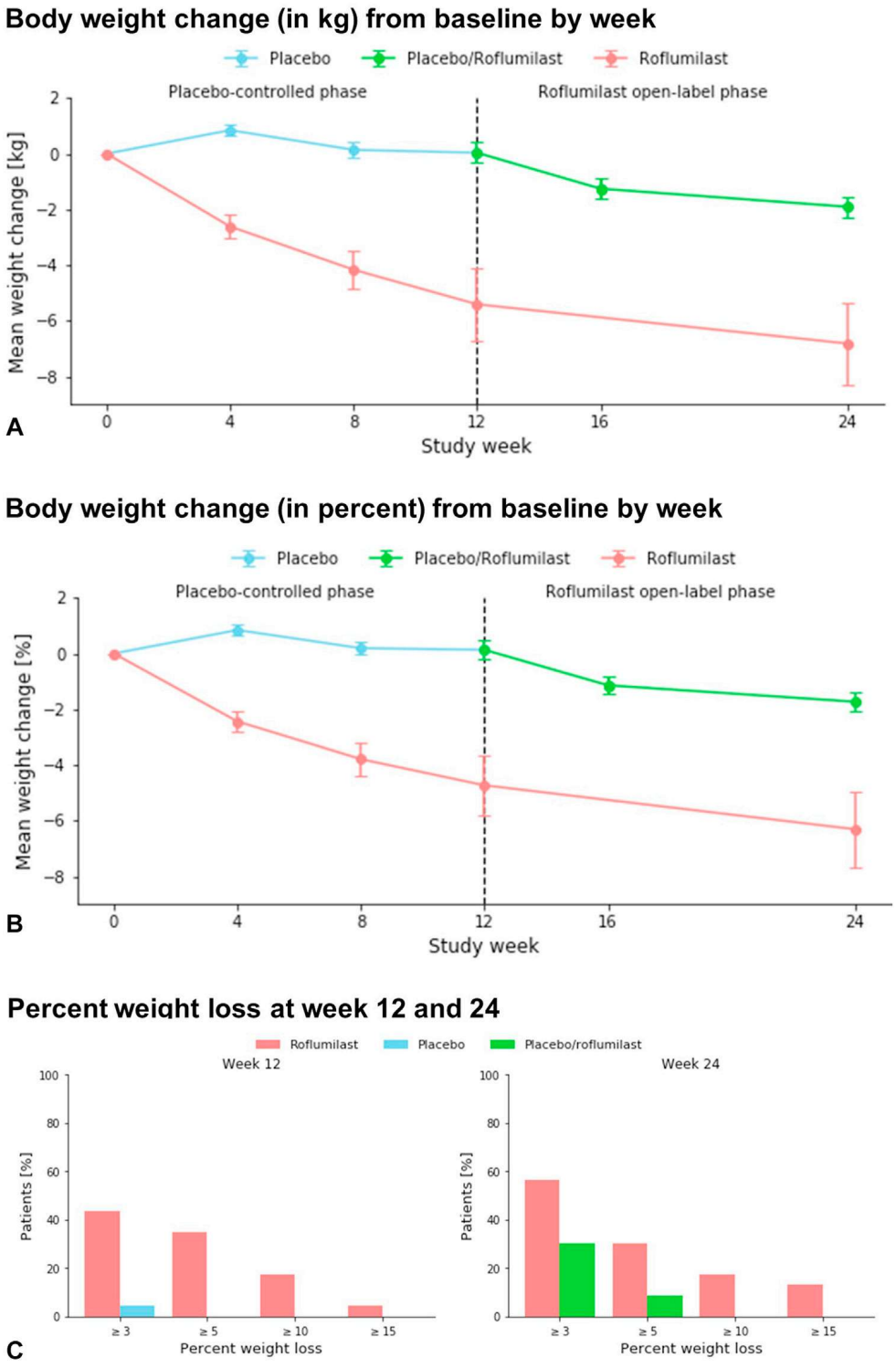

Fig 1. Psoriasis. Effect of oral roflumilast 500 μg once daily on body weight, as compared with placebo. **A** and **B,** Show the observed mean body weight change in kg and percent, respectively, over time. Error bars indicate 95% confidence intervals (CIs). **C,** Shows the observed percentages of participants who had body-weight reductions of at least 3%, 5%, 10%, and 15% from baseline to week 24.

In the roflumilast pivotal studies, COPD patients lost on average 2 kg of body weight with 1 year of active treatment compared to placebo.[15] In contrast to COPD, where malnutrition and underweight are common and even a small weight loss may be critical,[22-24] weight reduction is often favorable in

Table II. Body weight and cardio-metabolic outcomes, change from baseline

	Week 0-12 (Placebo-controlled phase)			Week 12-24 (Open-label phase)	
	Roflumilast *n* = 23	Placebo *n* = 23	*P*-value	Roflumilast until week 12 *n* = 23	Placebo until week 12 *n* = 23
Clinical parameters					
Body weight (kg), median (IQR)	−2.3 (−6.3; −0.8)	0.0 (−1.1; 2.2)	<.01	−3.2 (−7.7; −1.9)	−1.3 (−3.6; −0.3)
Body weight (kg), mean (SD)	−5.4 (7.7)	0.0 (2.2)	N/A	−6.8 (8.9)	−1.9 (2.3)
Body weight (%), median (IQR)	−2.6 (−6.3; −0.7)	0.0 (−1.0; 1.8)	<.01	−4.0 (−7.8; −2.0)	−1.3 (−3.4; −0.3)
Body weight (%), mean (SD)	−4.7 (6.3)	0.1 (2.1)	N/A	−6.3 (8.2)	−1.7 (2.2)
Body weight, *n*					
≥3%	10 (43)	1 (4)	.02	13 (57)	7 (30)
≥5%	8 (35)	0 (0)	.02	7 (30)	2 (9)
≥10%	4 (17)	0 (0)	.30	4 (17)	0 (0)
≥15%	1 (4)	0 (0)	1.0	3 (13)	0 (0)
Body mass index, kg/m^2	−0.8 (−2.1; −0.2)	0.0 (−0.4; 0.6)	<.01	−1.2 (−2.6; −0.7)	−0.5 (−1.0; −0.1)
Blood pressure, mmHg					
Systolic	−6 (14)	−4 (14)	.69	−6 (14)	−5 (14)
Diastolic	−3 (7)	−2 (13)	.78	−2 (8)	0 (12)
Pulse, beats/min	6 (7)	−5 (12)	.01	1 (8)	−3 (14)
Biochemistry					
HbA1c, mmol/mol	1 (−2; 2)	1 (−1; 2)	.21	0 (−2; 1)	1 (0; 2)
Total cholesterol, mmol/L	−0.1 (0.6)	0.1 (0.7)	.78	−0.1 (0.7)	−0.1 (0.6)
HDL cholesterol, mmol/L	0.0 (0.1)	0.0 (0.2)	.88	0.0 (0.1)	0.0 (0.2)
LDL cholesterol, mmol/L	0.0 (0.7)	−0.1 (0.5)	.78	0.0 (0.7)	−0.1 (0.6)
Triglycerides, mmol/L	−0.2 (0.8)	0.0 (1.0)	.99	−0.2 (0.8)	−0.1 (0.8)
Creatinine, μmol/L	2 (−3; 7)	0 (−6; 5)	.46	2 (−3; 7)	1 (−4; 6)
ALAT, U/L	−4 (20)	0 (17)	.47	−5 (23)	−5 (17)
hs-CRP, mg/L	0.0 (0.0; 2.0)	0.0 (−1.2; 0.0)	.28	0.0 (−0.8; 0.2)	0.0 (−0.9; 0.0)

Data are shown for all randomized patients. Categorical variables are presented in number and percentages. Numerical data are shown in mean and SD (normally distributed data) or median and IQR (non-normally distributed data).
ALAT, Alanine transaminase; *BMI*, body mass index; *HbA1c*, glycated hemoglobin A1c; *HDL*, high-density lipoprotein; *hs-CRP*, high-sensitivity C-reactive protein; *IQR*, interquartile range; *LDL*, low-density lipoprotein; *N/A*, not applicable; *SD*, standard deviation.

patients with psoriasis. Here, the average BMI is significantly higher compared to the general population.[25] In addition to the impact on cardiometabolic comorbidities, which are over-represented in patients with psoriasis,[1] body weight seems to have implications on psoriasis itself. Thus, weight loss by diet or exercise interventions is shown to reduce psoriasis severity, and gastric bypass is associated with an improved psoriasis prognosis.[5,26] In addition, psoriasis treatment may be more challenging in obese patients due to example related comorbidities, lower response rates, and higher costs with weight-adjusted drug doses. The causality between psoriasis and overweight/obesity is not fully elucidated, but increased levels of pro-inflammatory cytokines are known to play a key role in both conditions.[27]

The effect of roflumilast on glucose metabolism is sparsely investigated. It was, however, the focus of a large, randomized, placebo-controlled trial from 2012, where non-COPD patients with newly diagnosed type 2 diabetes (mean HbA1c 7.9%/63 mmol/mol) received oral roflumilast 500 μg or placebo once-daily for 12 weeks. In addition to lower fasting plasma glucose and improved postprandial glucose tolerance, mean HbA1c in the roflumilast group decreased 0.79%-points compared to baseline.[20] The HbA1c-reduction was significantly greater than in the placebo group (−0.33%-points). In the present study, no clinically significant biochemical changes were observed, including in HbA1c. It may be because HbA1c was already within the normal range at randomization (median HbA1c 35.0 mmol/mol in both treatment arms), or that the clinical effects of oral roflumilast on blood glucose are in fact minor. Overall, the lack of biochemical findings supports previously published safety data on the use of oral roflumilast for psoriasis,[8] and that regular blood

testing is not required after therapy initiation, according to the summary of product characteristics.

Strengths of the current trial include the company-independency, the randomized double-blinded design, the low discontinuation rates, and the very limited amount of missing data. Limitations are the secondary nature of the endpoints, a small sample size, and the relatively short study duration.

CONCLUSION

In conclusion, weight loss and reduced appetite were observed after 24 weeks of oral roflumilast therapy in patients with psoriasis. With psoriasis being a chronic disease strongly linked to overweight and obesity, the current findings support the growing evidence of oral roflumilast as an alternative treatment in patients with moderate-to-severe plaque psoriasis.

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Conflicts of interest

Dr Meteran received research funding from ALK-Abelló and honoraria as consultant and/or speaker for ALK-Abelló, GSK, Novartis, AstraZeneca, Sanofi-Aventis Denmark, and Teva. Skov received research funding from Almirall, Bristol-Myers Squibb, AbbVie, Janssen Pharmaceuticals, Sanofi, and the LEO Foundation, and honoraria as consultant and/or speaker for AbbVie, Eli Lilly, Novartis, Pfizer, LEO Pharma, Janssen Cilag, UCB, Almirall, Bristol-Myers Squibb, Boehringer Ingelheim, Novo Nordisk, and Sanofi, and is an investigator for AbbVie, Pfizer, Sanofi, Janssen Cilag, Boehringer Ingelheim, Eli Lilly, Novartis, Galderma, and LEO Pharma. Dr Zachariae is a paid speaker for Eli Lilly, Novartis, CSL, and LEO Pharma and a consultant and/or advisory board member for AbbVie, Janssen Cilag, Novartis, Eli Lilly, LEO Pharma, UCB, Almirall, Takeda, Amgen, Galderma, and CSL. Dr Knop served on scientific advisory panels, has been part of speaker's bureaus, served as a consultant to and/or received research support from 89bio, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Carmot Therapeutics, Eli Lilly, Gubra, Lupin, MedImmune, MSD/Merck, Mundipharma, Norgine, Novo Nordisk, Pharmacosmos, Sanofi, Structure Therapeutics, Zealand Pharma, and Zucara, and is a minority shareholder in Antag Therapeutics and co-owner of the weight loss clinic Medicinsk Vægttabsbehandling ApS. Dr Egeberg received research funding from Pfizer, Eli Lilly, Novartis, AbbVie, Boehringer Ingelheim, Almirall, and Janssen Pharmaceuticals, and consultant and/or speaker honoraria from AbbVie, Almirall, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, Eli Lilly and Company, Galderma, Galápagos NV, Horizon Therapeutics, Janssen Pharmaceuticals, LEO Pharma, Mylan, Novartis, Pfizer, Samsung Bioepis Co, Ltd, UCB, and Union Therapeutics. Drs Gyldenløve, Sørensen, Fage, and Nielsen have no conflicts of interest to declare.

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