CLINICAL TRIAL PROTOCOL

Drug	**Roflumilast (Daxas®)**
Protocol title	**Efficacy of roflumilast in the treatment of psoriasis – a randomised controlled trial**
EudraCT no.	**2020-000711-76**
H no.	**20013697**
Protocol date/version	**10.10.22 / V8.0_FINAL**

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PROTOCOL SYNOPSIS

Study title	**Efficacy of roflumilast in the treatment of psoriasis – a randomised controlled trial**
Drug	Roflumilast (Daxas®)
Compound	Phosphodiesterase (PDE)-4 inhibitor
Objective	To investigate the efficacy of roflumilast in the treatment of psoriasis
Design	Multicentre, double-blinded, randomised, placebo-controlled, clinical trial with open-label extension
Subjects	Patients ≥18 years with plaque psoriasis
Sample size	N = 40
Method	Twelve weeks treatment with either roflumilast or placebo tablets. Hereafter, both groups continue in open-label treatment (up to 96 weeks)
Primary endpoint	Proportion of patients achieving at least 75% reduction from baseline psoriasis area and severity index (PASI75) at week 12
Safety	Screening and monitoring according to national roflumilast guidelines
Study sites	Bispebjerg Hospital, University of Copenhagen, DK-2400 Copenhagen, Denmark. Gentofte Hospital, University of Copenhagen, DK-2900 Hellerup, Denmark. Aarhus University Hospital, DK-8200 Aarhus, Denmark
Key dates (expected)	Start of recruitment: January 2021 End of recruitment: January 2023 Last patient, last visit January 2026 Study termination January 2027

INTRODUCTION

Roflumilast (Daxas®), a selective, long-acting inhibitor of the enzyme phosphodiesterase-4 (PDE-4), is used in treatment of severe chronic obstructive pulmonary disease. Selective inhibition of PDE-4 inhibits the hydrolysis of cyclic adenosine monophosphate (cAMP) in inflammatory cells.[1] This increased availability of cAMP results in a wide range of anti-inflammatory effects, including decreased release of inflammatory mediators in neutrophils as well as decreased release of cytokines and reduction in tumour necrosis factor (TNF).[2]

Apremilast (Otezla®), another PDE-4 inhibitor, is currently approved for treatment of psoriasis and psoriatic arthritis. Furthermore, the drug has shown promise in other inflammatory diseases, including rheumatoid arthritis, and discoid and systemic lupus erythematosus.[3-5]

Since the chemical composition and mode of action for apremilast and roflumilast are closely related, it is reasonable to suspect that the two drugs possess the same therapeutic properties. This is supported by a recently published case report[6] and phase 1 study (topical formulation).[7]

The aim of this investigator-initiated trial is to study the efficacy of oral roflumilast in patients with plaque psoriasis. This has not previously been done.

DETAILED TRIAL DESCRIPTION

1. Study design

1.1 Objective

To investigate the efficacy of the PDE4-inhibitor roflumilast in patients with plaque psoriasis.

1.2 Treatment regimen

Patients are treated for 12 weeks with either roflumilast 500 microgram tablets once daily (marketed dose) or placebo tablets. In case of milder side-effects, e.g. nausea, after treatment initiation, the dose frequency may temporarily be reduced to every second day. After unblinding at week 12, both arms continue in additional 12 weeks open-label treatment for up to 96 weeks in total.

1.3 Primary endpoint

Proportion of patients achieving at least 75% reduction from baseline psoriasis area and severity index (PASI75) at week 12. PASI is a measure of psoriatic disease severity considering qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. PASI scores range from 0 to 72, with higher scores reflecting greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the regions is scored on a scale of 0 (none) to 6 (90% to 100% involvement).

1.4 Secondary endpoints

- Proportion of patients achieving at least 50% reduction in baseline PASI (PASI50) at week 12, 24, 48, 72, and 96
- Proportion of patients achieving at least 90% reduction in baseline PASI (PASI90) at week 12, 24, 48, 72, and 96
- Proportion of patients achieving 100% reduction in baseline PASI (PASI100) at week 12, 24, 48, 72, and 96
- Percent change from baseline in PASI score at week 12, 24, 48, 72, and 96
- Change (1 or more points) in static physician global assessment (sPGA) at week 12, 24, 48, 72, and 96. The sPGA is a 5-point scale ranging from 0 (clear, except for residual discoloration) to 4 (severe; majority of plaques with severe thickness, erythema, and scaling). Scores for thickness, erythema and scaling are summed and the mean of these 3 scores equals the overall sPGA score. Fractional values for the sPGA are rounded to the next highest integer (e.g. a score of 3.5 is rounded to 4; 3.4 is rounded to 3).
- Percentage change from baseline in affected body surface area (BSA) at week 12, 24, 48, 72, and 96. Overall BSA affected by psoriasis is estimated by comparison of the size of the affected area to the palm area of the patient's hand (entire palmar surface or 'handprint'), which equates to approximately 1% of total BSA.

- Percentage change from baseline in the product of BSA (%) and the sPGA, which is considered as the total psoriasis severity index at week 12, 24, 48, 72, and 96
- Change from baseline in dermatology life quality index (DLQI) at week 12, 24, 48, 72, and 96. DLQI is a validated, self-administered, 10-item questionnaire that measures the impact of skin disease on patients' quality of life, based on recall over the past week. Domains include symptoms, feelings, daily activities, social, leisure, work or studying, personal relationships, and treatment. Each question is answered on a scale of 0 (not at all) to 3 (very much); total DLQI score ranges from 0 to 30. A DLQI score greater than 10 is indicative of severe psoriasis.
- Adverse events (AEs), serious adverse events (SAEs), serious adverse reactions (SARs), and suspected unexpected serious adverse reactions (SUSARs) (see 4.3 and appendix)

2. Study population

2.1 Subjects

A total of 40 patients with plaque psoriasis are included in the study. Patients will be recruited online (e.g. forsoegsperson.dk), from study sites, and dermatology private practices. Before any trial related procedures are performed, patients are thoroughly informed in an undisturbed room about the study and he/she must sign and date the informed consent form. Patients are offered at least 24 hours to consider their participation in the study.

2.2 Randomization and blinding

Patients are randomized 1:1 to treatment with roflumilast or placebo. The randomization will be carried out by an online randomization generator. The drug/placebo supplier is responsible for labelling and blinding of tablets.

2.3 Inclusion criteria

- Age ≥18 years
- Chronic stable plaque psoriasis (min duration 6 months)
- PASI ≥ 8
- Body mass index (BMI) ≥ 20 kg/m^2
- Candidate for systemic treatment of psoriasis
- Negative pregnancy test (only women)
- Safe anticonception during entire study and at least 1 week after end of treatment (~5 times plasma half-life of roflumilast)

2.4 Exclusion criteria

- Severe immunological disease, e.g. HIV, systemic lupus, and systemic sclerosis
- Current tuberculosis
- Current viral hepatitis
- Heart failure (NYHA III-IV)
- Moderate or severe liver failure (Child-Pugh B-C)

- Current or former malignancy (basal cell carcinoma excluded)
- Current or former depression with suicidal ideation
- Topical therapy for psoriasis 2 weeks before randomization and during study
- Systemic therapy for psoriasis or psoriatic arthritis 4 weeks before randomization and during study
- Current treatment with theophylline, phenobarbital, carbamazepine, or phenytoin
- Previous treatment with apremilast (Otezla®)
- Allergy to lidocaine or carbocaine
- Confirmed pregnancy
- Planned pregnancy within 6 months
- Breast feeding
- Blood donation during study
- Inability to complete study

2.5 Patient withdrawal

Patients can withdraw from the trial at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason for withdrawal may e.g. be withdrawal of consent, adverse event(s), pregnancy or relevant disease discovered during the trial (see exclusion criteria), or loss to follow-up. Drop-outs will be replaced until 40 patients have completed 3 months treatment. Patients withdrawing from the trial will be encouraged to go through the same final evaluations as patients completing the trial according to protocol. Data from dropouts will be included in data processing.

3. Paraclinical examinations

3.1 Blood analyses

- Albumin
- Alanine transaminase (ALAT)
- Basic phosphatase
- Bilirubin
- Calcium
- Cholesterol
- COVID-19 serology
- Creatinine
- Estimated glomerular filtration rate (eGFR)
- Fibrinogen
- Haemoglobin
- Haemoglobin A1c
- Human chorionic gonadotropin (hCG)
- Hepatitis A, B and C
- High-sensitivity C-reactive protein (hs-CRP)

- Inflammation marker panel (e.g. tumour necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and interleukin 19 (IL-19))
- HIV
- INR
- Lactate dehydrogenase (LDH)
- Leucocytes
- Natrium
- Potassium
- Thrombocytes
- Quantiferon test
- Vitamin D
- HLA-Cw6 (NPU59005)

A maximum of 500 ml. venous blood is collected in total from each patient in order to provide baseline data and monitor patients during the study. Samples are analysed at the Department of Clinical Biochemistry at study sites according to standard procedures. Non-routine blood analyses (e.g. interleukins) will have to be analysed in specialized research labs. This will take place at latest at study termination. Any excess material will be destructed, i.e. extra material is not collected for future research projects.

3.2 Physical examination

- PASI
- BSA
- sPGA
- Height
- Waist- and hip circumference
- Weight
- Blood pressure and pulse

3.3 Pulmonary function tests

As roflumilast is currently marketed for chronic obstructive pulmonary disease, it is relevant to evaluate changes in lung function during the study. Three types of pulmonary function tests are performed:

- **Spirometry**

  Most common pulmonary function test. Measures forced expiratory volume during first second (FEV1) and forced volume capacity (FVC). The FEV1/FVC-ratio is used to diagnose obstructive and restrictive lung disease. Two acceptable and reproducible measurements are required before the test is completed. A test takes approx. 5 min. Spirometry is a non-invasive and safe test. However, some people may briefly feel dizzy or tired afterwards. The test will be performed according to ATS/ERS guidelines[8].

- **Forced oscillation test (FOT)**
  Forced oscillation technique is a non-invasive method to measure respiratory mechanics by resistance and reactance during spontaneous ventilation. Hence, FOT differs from spirometry as it does not require forced respiratory manoeuvres. FOT distinguishes airway dysfunction in the small and large airways and recent studies have shown that FOT is more sensitive in detecting small airway disease than spirometry[9]. The FOT is a safe procedure, lasts approx. 5 min, and has or no side effects.
- **Fractional concentration of exhaled nitric oxide (FeNO) test**
  A way to determine the level of eosinophilic lung inflammation. It is performed using a portable device that measures levels of nitric oxide in exhaled air. The test is non-invasive and safe and takes approx. 30 seconds.

3.4 Skin biopsies

After injection of local anaesthesia, two 3 mm punch biopsies (lesional and peri-lesional) are taken from min. n=20 patients at week 0. At week 4, 12, and 24, only lesional biopsies are taken. Biopsies are either fixed with formalin for histopathological evaluation (e.g. hematoxylin and eosin staining) or snap-frozen for RNA analyses.

3.5 Questionnaires

- DLQI
- Beck depression inventory (BDI) II
- Numeric rating scale (NRS)-pain, joints
- Numeric rating scale (NRS)-morning stiffness > 30 min.
- Numeric rating scale (NRS))-pain, skin
- Numeric rating scale (NRS)-itch

4. Study drug and safety

4.1 Drug supply

Roflumilast 500 microgram tablets (blinded and open-label) and placebo tablets are requested from The Hospital Pharmacy, The Capital Region of Denmark, and supplied to patients free of charge from the participating departments.

4.2 Side effects

Side effects attributed to roflumilast are mainly gastrointestinal. Most common adverse events include decreased appetite, weight loss, abdominal pain, diarrhoea, nausea, vomiting, headache, and insomnia. Less commonly, patients may experience muscle weakness, anxiety, vertigo, tremor, and hypersensitivity. Very rarely (0,01-0,1%), haematochezia, gynaecomastia, depression, nervousness, angioedema, and upper airway infections have been reported. The roflumilast product summary is used as reference document when evaluating side effects.

4.3 Reporting of adverse reactions

Please see appendix

4.4 Unblinding

Emergency randomization codes are kept at all sites. If a patient develops adverse events that demand knowledge on the treatment, the code will be broken for that patient only. Any assessment to unblind will be made in consultation with the clinical team and research team. Final decisions to unblind rest with the clinicians treating the patient, not the research team.

4.5 Drug accountability

Patients will be administering the medication at home. All patients are carefully instructed how to take roflumilast/placebo. The quantity of study drug given to patients will be registered and documented in the trial master file (TMF) and in the clinical report form (CRF) to ensure correct administration. Patients will be asked to return empty drug boxes. Returned study drugs are destructed according to standard procedures.

4.6 Insurance

Participation in the study is covered by the Patient Compensation Association.

4.7 Rescue medication

In case of flare-up, treatment with topical steroids or calcineurin inhibitors can be accepted (PI decision). Type, dosage and amount (grams) will be recorded in the eCRF.

5. Data management

5.1 Collection

All collected source data are registered in individual paper-CRFs located at respective study sites and online (e.g. REDCap). Information on participation and SAEs related to the study treatment are documented in both CRFs and patient hospital files.

5.2. Source data verification

To ensure data completeness and accuracy, source data verification is performed. This requires reviewing of relevant parts of patient hospital files, in particular previous dermatologic treatments and current medication. Patients are informed in writing about the purpose and need for source data verification. Patient files are not reviewed before the informed consent is obtained.

5.3 Data storage

Source data, source documents, trial protocol and amendments, drug accountability forms, correspondence, patient identification lists, informed consent forms, and other essential GCP documents will be retained at Bispebjerg Hospital for at least 5 years after the study is completed.

5.4 Statistics

Data analyses are performed using Python version 3.7.6 including relevant packages (Python Software Foundation) and the statistical software R version 4.2.0 (The R Foundation). Continuous variables are presented as means and standard deviations (SD) (normally distributed data) or medians and interquartile ranges (IQR) (non-normally distributed data). Categorical variables are reported as frequencies and percentages. Efficacy data is assessed by intention to treat (ITT). Binary outcomes are presented as frequencies with percentages, whereas continuous outcomes are presented as ranges. Missing data are handled with non-responder imputation (NRI) when specified, otherwise last observation carried forward (LOCF) is used. The primary study outcome, PASI75, and secondary outcomes are analyzed with Fisher's exact test and analyses of covariance (ANCOVA) with baseline value as covariate. The Benjamini-Hochberg procedure is used to adjust p-values for multiple testing. The time to achieve PASI50, PASI75, and PASI90 is visualized. Adverse events are reported as number and percentages of patients as well as exposure adjusted incidence rates (EAIR) per 100 patient years. All tests are carried out at a significance level of 0.05

5.5 Calculation of sample size

Based on clinical psoriasis improvement in the apremilast phase 2 study and assuming roflumilast and apremilast are equally effective, a total of 40 patients must complete the trial (20 patients in each treatment arm). This provides 80% power to detect a difference between roflumilast and placebo treatment. In-vitro studies have found roflumilast to be up to 90 times more potent than apremilast (equipotent doses), and the trial may therefore have higher power than the calculated 80%.

5.6 Scientific publication

At the end of the trial one or more manuscripts are prepared for publication in a scientific journal. All results whether negative, positive, or inconclusive will be published. The results may moreover be presented as posters or oral presentations at national and/or international conferences. The final decision on the order of authorship are decided when the study has been finalized.

6. Approvals/notifications

6.1 Ethics committee

The protocol, including subject information and informed consent form, is approved by the regional ethics committee. The investigators ensure that the study is conducted in conformance with the Edinburgh, Scotland (2000), amendment to the Declaration of Helsinki 1964, and with national laws and regulations for clinical research.

6.2 Danish Data Protection Agency

The trial is notified to the Danish Data Protection Agency and performed according to 'Databeskyttelsesforordringen' and 'Databeskyttelsesloven'.

6.3 Danish Medicine Agency

The trial is notified to the Danish Medicines Agency. As part of the mandatory inspection of clinical trials, the Danish Medicines Agency is allowed to access collected study data and medical files.

6.4 Good Clinical Practice (GCP)

The trial is monitored by the GCP-unit at University of Copenhagen

6.5 Market authorization holder

The market authorization holder of roflumilast in Denmark has been informed about the trial.

7. Ethical considerations

Most common adverse events to treatment with roflumilast are mild to moderate, transient gastrointestinal symptoms and headache. All paraclinical examinations are routine procedures. When collecting blood and skin biopsies, some patients may experience minor discomfort/pain, a small bleeding, or local infection. The skin biopsies will leave a tiny scar (few mm in size). The lung function tests are safe, non-invasive and quick to perform. At the end of the study all patients will be offered conventional psoriasis treatment according to national guidelines.

8. Financing

The trial is financially supported by the participating departments, and in addition, applications will be sent to private funds. The regional ethics committee will be notified if grants are provided. The market authorization holder of roflumilast is not involved in the study. None of the investigators hold any financial interest in roflumilast.

9. Appendices

- Adverse reactions
- DLQI
- Beck depression inventory (BDI) II

PRACTICAL TREATMENT PROCEDURE

RECRUITMENT

Patients are contacted at study sites and by advertising. Eligible patients that show interest in participating are given thoroughly verbal and written information by an investigator about the purpose, nature, possible risks, and benefits of the trial. Patients are offered to bring an assessor, to have at least 24 hours reflection, and to ask questions before signing the consent declaration. All trial investigators have experience with psoriasis and clinical research.

RANDOMISED CONTROLLED TRIAL

Screening visit

According to 'Study flow chart' (p. 15). If all inclusion criteria are met, an appointment for week 0 visit is set up.

Duration: 30 min

Week 0 visit

According to 'Study flow chart' (p. 15)

Visit duration: 60 min

Week 4 and 8 visit

According to 'Study flow chart' (p. 15)

Visit duration: 20 min

Week 12 visit

According to 'Study flow chart' (p. 15). Patients are unblinded and continue in open-label treatment.

Visit duration: 60 min

OPEN-LABEL EXTENSION

Week 16 visit

Only applies for patients in placebo-arm. According to 'Study flow chart' (p. 15).

Visit duration: 20 min

Week 24 visit

According to 'Study flow chart' (p. 15)

Visit duration: 30 min

Week 36 visit and following every other 12 weeks (until week 96)

According to 'Study flow chart' (p. 15)

Visit duration: 30 min

Study flow chart		Screening	Week 0	Week 4	Week 8	Week 12	Week 16*	Week 24	Week 36 (+)
Interview	Introduction	x							
	Informed consent	x							
	Medical history	x							
	Current medication	x							
	Smoking habits		x						
	Dermatology life quality index (DLQI)		x	x	x	x	x	x	x
	Beck Depression Inventory (BDI) II	x		x	x	x	x	x	x
	Numeric rating scales (NRS)		x	x	x	x	x	x	x
Clinical examinations	Psoriasis area and severity index (PASI)	x		x	x	x	x	x	x
	Static Physician global assessment (sPGA)		x	x	x	x	x	x	x
	Body surface area (BSA)		x	x	x	x	x	x	x
	Nails		x					x	x
	Blood pressure and pulse	x				x		x	x
	Height	x							
	Weight	x		x	x	x	x	x	x
	Waist and hip circumference		x			x		x	x
Lung function tests	Spirometry		x			x		x	x**
	FOT		x			x		x	x**
	FeNO		x			x		x	x**
Biopsies	Lesionel skin biopsies		x	x		x		x	
	Peri-lesionel skin biopsies		x						
Blood samples	Routine	x	x	x	x	x	x	x	x
	Biobank		x	x	x	x		x	x
Medication	Randomisation		x						
	Administration of tablets		x	x	x	x	x		
	Collection of empty boxes			x	x	x	x	x	x
	Unblinding					x			
Safety	Control of blood samples	x	x	x	x	x	x	x	x
	Adverse events			x	x	x	x	x	x
	Compliance			x	x	x	x	x	x

* Only applies for patients in placebo-arm; ** At week 48, 72, and 96

ABBREVIATIONS

AE	Adverse events
BDI II	Beck depression inventory II
BMI	Body mass index
BSA	Body surface area
cAMP	Cyclic adenosine monophosphate
CRF	Clinical report form
DLQI	Dermatology life quality index
FEV1	Forced expiratory volume during first second
FOT	Forced oscillation test
FVC	Forced volume capacity
GCP	Good clinical practice
Hs-CRP	Highly sensitive c-reactive protein
IL	Interleukin
NRS	Numeric rating scale
PASI	Psoriasis area and severity index
PASI50	Proportion of patients achieving at least 50% reduction in baseline PASI
PASI75	Proportion of patients achieving at least 75% reduction in baseline PASI
PASI90	Proportion of patients achieving at least 90% reduction in baseline PASI
PASI100	Proportion of patients achieving at least 100% reduction in baseline PASI
PDE4	Phosphodiaesterase-4
SAE	Serious adverse event
SAR	Serious adverse reaction
sPGA	Static physician global assessment
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial master file
TNF	Tumour necrosis factor

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