Clinical Trial Protocol

Effect of brodalumab compared to placebo on vascular inflammation in moderate-to-severe psoriasis

A randomised, double-blind, placebo-controlled, trial to evaluate the efficacy of brodalumab monotherapy on vascular and systemic inflammation by 18F-FDG-PET/CT in subjects with moderate-to-severe plaque-type psoriasis who are candidates for systemic therapy

This study protocol has been prepared in accordance with the guidelines for GCP (ICH-GCP and danish Executive Order number 695 of 12/06/2013). All aspects of the study including planning, completion and reporting are carried out in accordance with GCP as well as national and international legislation and provisions. The study is monitored by the GCP unit at Aarhus University Hospital.

Department of Dermatology Aarhus University Hospital		
	Sponsors protokolkode	**PsoPET2**
	Central Denmark Region Ethical Comittee No.	**1-10-72-386-17**
	EudraCT No.	**2017-003697-14**
	Danish Medicines Agency No.	**2017093879**
	Date	**23.02.2018**

1 Clinical Trial Approval Statement

1.1 Approval statement sponsor

The following person has approved this clinical trial protocol:

Lars Iversen, MD, DMSc
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1.2 Approval statement investigator

The following persons has approved this clinical trial protocol:

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1.3 Approval statement co-investigator

The following person has approved this clinical trial protocol:

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1.4 GCP responsibilty

The following persons take responsibility for enabling GCP monitoring:

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3 Trial Identification

The Danish Data Protection Agency	
Central Denmark Region Ethical Comittee	**1-10-72-386-17**
EudraCT	2017-003697-14
Danish Medicines Agency	**2017093879**
ClinicalTrials.gov	

4 Trial location

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5 Funding

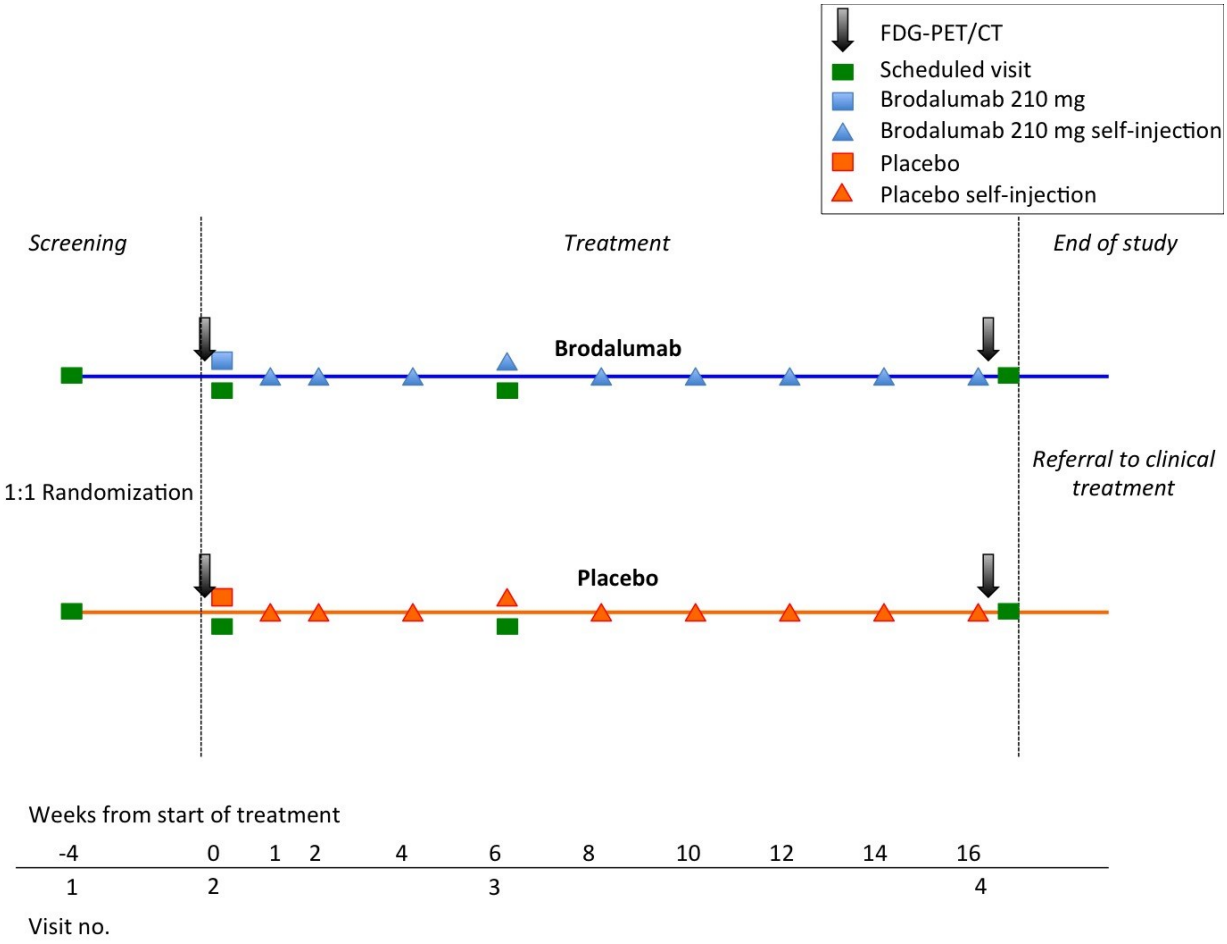
This investigator initiated clinical trial is supported by a grant provided by LEO Pharma. The investigational medicinal product (Brodalumab) is provided by LEO Pharma. LEO Pharma has no influence on the design of the study, the collection of data, and will have no influence on the interpretation of the results, the preparation of the manuscripts or the decision to submit for publication.
The grant will be transferred to an account at Aarhus University Hospital. Trial related expenses will be paid from this account. The total amount received from LEO Pharma to cover trial related expenses in this investigator initiated study is 212.900 euro.

6 List of abbreviations:

AE:	Adverse events
BMI:	Body mass index
CAC:	Coronary artery calcium
CAD:	Coronary artery disease
CCTA:	Contrast-enhanced computed tomography angiography
CD:	Cluster of Differentation
CI:	Confidence interval
eCRF:	Electronic case report form
CRP:	C-reactive protein
CT:	Computed tomography
DLQI:	Dermatology Life Quality Index
DMA:	Danish Medicines Agency
EANM:	European Association of Nuclear Medicine
ECG:	Electrocardiogram
EMA:	European Medicines Agency
EOW:	Every other week
FDG:	^{18}F–fluorodeoxyglucose
GCP:	Good Clinical Practice
HCP:	Health care professional
HIV:	Human immunodeficiency virus
HLA:	Human leukocyte antigen
hs:	High-sensitivity
ICH:	International Council for Harmonisation
IGA:	Investigator's global assessment
IL:	Interleukin
IFN:	Interferon
IgG:	Immunoglobulin G
IMP:	Investigational Medicinal Product
LDL:	Low-density lipoprotein
MBq:	Megabecquerel
MHC:	Major histocompatibility complex
MI:	Myocardial infarction
mSv:	milliSievert
NF:	Nuclear Factor
PASI:	Psoriasis Area Severity Index
PET:	Positron emission tomography
PsA:	Psoriatic arthritis
PSI:	Psoriasis symptom inventory
PUVA:	Psoralen ultraviolet type A
RA:	Receptor A
RCT:	Randomised controlled trial
ROI:	Region of interest
SAE:	Serious adverse event
Sv:	Sievert
SD:	Standard deviation

SLR: Spleen-to-liver ratio
SUV: Standardised uptake values
TBR: Target-to-background ratio
TNF: Tumour necrosis factor
UVA: Ultraviolet type A
UVB: Ultraviolet type B
VAS: Visual analog scale
VOI: Volume of interest

6 Flow diagram of trial design



7 Schedule of procedures

Visit	Screen 1	Visit 2	Visit 3	Visit 4
Week	-4	0	6	16
Office visits				
Informed consent	X			
Demographics	X			
Inclusion/exclusion criteria	X			
Diagnosis of PsA	X			
Smoking/alcohol consumption	X			
Psoriasis: medical history / previous psoriasis therapies	X			
Other medical history / treatments	X			
Concomitant medications	X	X		X
Randomization	X			
Collection of adverse events			X	X
Physical examination				
General physical examination	X			X
Height	X			
Weight	X			X
Hip circumference	X			
Blood pressure, pulse	X			X
PASI	X	X	X	X
BSA	X	X	X	X
IGA	X	X	X	X
Quantitative nail assessment	X	X	X	X
Quantitative joint assessment	X	X	X	
DLQI	X	X	X	X
PSI	X	X	X	X
VAS (joints)	X	X	X	X
Labs				
Serum electrolytes + renal panel	X	X	X	X
Acute-phase proteins	X	X	X	X
Lipids	X	X		X
Liver enzymes	X	X		X
Glucose metabolism	X	X	X	X
T-spot	X			
HIV I+II	X			
Hepatitis serology	X			
Treatment				
Initiation of treatment / placebo		X		
Procedures				
FDG-PET/CT		X		X
Chest X-ray	X			
Optional punch biopsy		X	X	

8 Introduction, background, and rationale

8.1 Psoriasis

Psoriasis is a common inflammatory disease of the skin and joints with a prevalence of 2%-4% in the Western population with varying prevalence among different ethnic groups.[1,2] Accounting for 90% of cases, chronic-plaque psoriasis (henceforth "psoriasis") is the most common form of the disease.

Population-based studies report a genetic predisposition to psoriasis, showing a higher prevalence of psoriasis among first- and second-degree relatives than in the general population.[3]

The characteristic clinical features of psoriasis are explained by the histopathological changes: Hyper-proliferation of the basal keratinocytes and the dermal infiltrate cause the skin to thicken; parakeratosis with premature maturation of keratinocytes and retention of nuclei in the stratum corneum cause scaling; and hyperaemia due to the dilated and winding capillaries in combination with inflammation causes the reddening of the skin.[4]

Previous research has established that the disease is mainly a dendritic cell and T-cell-mediated disease with complex feedback loops from antigen-presenting cells, neutrophilic granulocytes, keratinocytes, vascular endothelial cells and the cutaneous nervous system.[5] Traditionally, interleukin (IL)-12-stimulated T-helper lymphocyte (Th)-1 development has been viewed as an important driver for psoriasis pathogenesis, but in recent years it has become increasingly evident that the IL-23/Th-17 axis is of great importance.[6] Once activated, Th-17 cells secrete various isoforms of IL-17 and IL-22, which constitute the link to epidermal hyper-proliferation.

Overall, in the current models, the central features of immunogenicity in psoriasis are heavily based on IL-17 production by Th-17 cells and their IL-23-induced expansion and feedback loops, with TNF-α/NF-kappa beta signalling and signalling through Th22 and CD8+ Tc17 cells as other important contributing pathways.

8.2 Psoriasis and cardiovascular disease

Studies in different populations in the Western world have repeatedly shown that psoriasis is associated with an increased risk of cardiovascular comorbidity. The data on which these studies build come from various sources, including nation-wide registers, large insurance databases, research databases and hospital cohorts.[7-11] In moderate-to-severe psoriasis, the risk levels are broadly at a level corresponding to the risk found in rheumatoid arthritis, which was confirmed by at least one study that compared the risk of major cardiovascular events in psoriasis and rheumatoid arthritis.[11] Several meta-analyses show that psoriasis is associated with an increased risk of cardiovascular disease.[12-14] Taken together, this indicates that the relative risk of cardiovascular disease is increased in patients with severe disease and early disease onset, and that older patients with severe psoriasis have a high, absolute risk of cardiovascular disease.

The inflammatory pathways of psoriasis are much similar to those identified in atherosclerosis. There is evidence of systemic inflammation in psoriasis,[15,16] and an association between psoriasis and cardiovascular disease due to accelerated coronary artery

disease is suspected.[17,18] It has been suggested that subcutaneous adipose tissue inflammation contributes to the pathogenesis of psoriasis, and there is evidence in support of an immune cell–adipocyte crosstalk in the pathogenesis of inflammatory diseases as well as in metabolic comorbidities.

The concept of atherosclerosis as an inflammatory disease is based on observations of immune activation in human atherosclerotic lesions, recognition of inflammatory biomarkers as independent risk factors for cardiovascular events and evidence of immune activation induced by low-density lipoproteins.

We have previously shown that 13 months of clinically effective treatment of psoriasis predominantly with anti-TNF drugs ameliorates the progression of CAD in patients with moderate-to-severe psoriasis.[19] These data corroborate the results of other epidemiological and clinical studies. Taken together, there is emerging evidence that treatment of psoriasis with biologic agents is associated with a reduced risk of death and major cardiovascular events; and a reduction of surrogate markers such as endothelial dysfunction, insulin sensitivity, CRP and carotid intima thickness. Furthermore, recent data suggest an improvement of coronary flow reserve[20] and improved myocardial function following treatment with biologic agents.[21]

Interleukin (IL)-17 has been shown to be atherogenic in animal models and involved in the recruitment of inflammatory cells to atherosclerotic plaques, a process inhibited by depleting IL-17.[22,23] However, the potential of IL-17 blocking agents to improve atherosclerosis in humans has only been sparsely investigated. One ongoing clinical study is investigating the effect of IL-17A antibodies compared to placebo on aortic vascular inflammation in subjects with moderate to severe plaque psoriasis (clinicaltrials.gov identifier: NCT02690701).

Previous studies have shown that treatment with brodalumab, an IL-17 receptor A blocking agent (IL-17RA), resulted in a rapid and highly effective reduction in the signs and symptoms of psoriasis.[24]

However, the effect of IL-17RA on vascular inflammation and cardiovascular outcomes is unknown.

8.3 ^{18}F–fluorodeoxyglucose positron emission tomography computed tomography

^{18}F–fluorodeoxyglucose (FDG) positron emission tomography (PET) computed tomography (CT) provides a direct measure of metabolic activity in vessels and other tissues. FDG is a radiolabelled glucose analogue taken up in tissues with high metabolic activity such as inflammatory active tissue and tumour cells. Traditionally, FDG-PET/CT has been used in oncology, but given the focus of inflammation as a key player in atherosclerosis and the need to better diagnose active disease, vascular FDG-PET imaging has gained increasing interest as a promising tool for imaging atherosclerotic plaque inflammation and vulnerability.[25] In early proof-of-concept studies it was shown that FDG accumulates in macrophage-rich atherosclerotic plaques and demonstrated that vascular macrophage activity can be quantified noninvasively with FDG-PET.[26] In addition to visualizing atherosclerotic plaque inflammation, it has been shown that FDG uptake is associated with the severity of inflammation in atherosclerotic plaques.[27, 28] Furthermore, arterial FDG uptake increases in proportion to atherosclerotic risk factors, with plaque morphological complexity, and after

atherothrombotic events. [29] It has been shown that FDG-PET/CT significantly improves cardiovascular disease prediction beyond that of traditional risk factor scoring and that FDG-PET/CT imaging provides prognostic information adding to that which may be obtained using soluble biomarkers [30-33].

We have previously conducted a clinical study evaluating vascular and subcutaneous adipose tissue inflammation from FDG-PET/CT.[34] In this study we found that arterial inflammation was increased in psoriasis patients compared to controls (mean (SD) whole vessel maximal target-to-background ratio (TBR_{max}) 2.46 [0.31] versus 2.09 [0.36]; *P*=0.005). In psoriasis patients, higher FDG uptake values were observed for all aortic segments except the ascending aorta. Subcutaneous adipose tissue FDG uptake was increased in psoriasis patients compared with controls (mean TBR_{max} 0.49 [0.18] versus 0.31 [0.12]; *P*=0.002; and mean $TBR_{max\text{-}10pixels}$ 0.39 [0.10] versus 0.28 [0.12]; *P*=0.01). Our results are corroborated by other studies.[35,36]

Furthermore, we have recently conducted a study demonstrating increased splenic inflammation in patients with psoriasis compared with age-matched control subjects. Additionally, a significant association between splenic inflammation and aortic wall inflammation was found in psoriasis patients (unpublished data). Other exploratory studies indicate a role of the spleen in atherosclerosis-associated immunity,[37,38] and cardiovascular clinical studies indicate that a cardio-splenic axis exists.[39] Given the well-established role of the spleen in systemic inflammatory diseases, this provides evidence of systemic inflammation in psoriasis beyond that reported by biomarker studies.

Recently, in an opel-label cohort of patients with mild-to-moderate psoriasis it was shown that reduction of skin inflammation by mixed interventions was associated with improvement in aortic wall inflammation assessed by FDG-PET/CT.[40] This finding was not corroborated by two RCT's assessing the effect of anti-TNF drug adalimumab on aortic wall inflamation as no significant difference was found after 16 weeks of treatment.[41,42] However, a limitation of these studies were that the primary endpoint was changes in FDG-uptake in only the ascending part of aorta and not the entire vessel.[43] Choosing the ascending aorta as the representative aortic segment may not always be the optimal approach. For example, Besson et. al. investigated the performance of different semiquantitative measures to distinguish controls from patients with large vessel vasculitis and found that TBR performed well in all segments of the aorta – except in the ascending aorta.[44] In line with this, we also recently found increased aortic wall inflammation in psoriasis patients compared with controls without inflammatory diseases in all segments of the vessel except the ascending part.[34] It has previously been suggested that whole-vessel aortic mean TBRmax is well suited as a marker of cardiovascular risk for assessment of global arterial inflammation.[45]

Taken together, these studies establish FDG-PET/CT as a feasible technique for visualizing vascular inflammation and systemic inflammation as well as changes in vascular/systemic inflammation in psoriasis.

8.4 Experience with experimental medicinal product

Brodalumab is a recombinant fully human monoclonal immunoglobulin IgG2 antibody that binds with high affinity to human IL-17RA and blocks the biological activities of the pro inflammatory cytokines IL-17A, IL-17F, IL-17A/F heterodimer and IL-17C and IL-17E (IL-25).

Brodalumab is approved for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy. The trade name of brodalumab in Europe is Kyntheum and it is marketed by LEO Pharma A/S. Kyntheum is available as a 210 mg solution for injection.

The approval of brodalumab is based on the results of three multicenter, randomized, double-blind, controlled trials (AMAGINE 1, 2, and 3) that enrolled a total of 4373 subjects 18 years of age and older with at least a 6-month history of moderate to severe plaque psoriasis, defined as having a minimum affected body surface area (BSA) of 10%, a Psoriasis Area and Severity Index (PASI) score ≥ 12, a static Physician's Global Assessment (sPGA) score ≥3 in the overall assessment (plaque thickness/induration, erythema, and scaling) of psoriasis on a severity scale of 0 to 5, and who were candidates for systemic therapy or phototherapy. In all three trials, subjects were randomized to subcutaneous treatment with placebo or brodalumab 210 mg at Weeks 0, 1, and 2, followed by treatments every 2 weeks through Week 12. In the two active comparator trials (AMAGINE 2 and 3), subjects randomized to ustekinumab received a 45 mg dose if their weight was less than or equal to 100 kg and a 90 mg dose if their weight was greater than 100 kg at Weeks 0, 4, and 16, followed by the same dose every 12 weeks.
At week 12, the proportion of patients attaining a 75% improvement from the baseline Psoriasis Area and Severity Index (PASI 75) was similar among the three phase III trials (AMAGINE-1, 83%; AMAGINE-2, 86%; AMAGINE-3, 85%). Brodalumab remained efficacious through 52 weeks of treatment.[46]
Most common adverse reactions (incidence ≥1%) were arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection site reactions, influenza, neutropenia, and tinea infections.
Suicidal ideation and behavior, including 4 completed suicides, occurred in subjects treated with brodalumab in the psoriasis clinical trials. There were no completed suicides in the 12-week placebo-controlled portion of the trials. Brodalumab users with a history of suicidality or depression had an increased incidence of suicidal ideation and behavior as compared to users without such a history. A causal association between treatment with brodalumab and increased risk of suicidal ideation and behavior has not been established.
Brodalumab is contraindicated in patients with active Crohn's disease and should be used with caution in patients with a history of Crohn's disease because brodalumab may cause worsening of disease.
Further details are available from the product description (Appendix I).

8.5 Trial rationale and hypothesis

We hypothesize that aortic wall inflammation is increased in subjects with moderate-to-severe psoriasis and that this inflammatory process may be reduced by effectively treating psoriasis by brodalumab. Furthermore, we hypothesize that systemic inflammation, as indicated by increased splenic FDG uptake, may be reduced by brodalumab therapy, and that this reduction may be associated with reduced aortic wall inflammation. The rationale for the duration of follow-up is based on previous clinical trials showing a rapid and effective response to brodalumab on signs and symptoms of psoriasis.

The purpose of the study is to assess the effect of IL-17RA blockade by brodalumab on aortic wall inflammation and splenic inflammation in patients with moderate-to-severe psoriasis.

8.6 Perspective

The results of this study may advance the knowledge of vascular inflammation in psoriasis, which may be an important link between skin inflammation, systemic inflammation, and cardiovascular comorbidities. If vascular inflammation is abrogated by effectively treating psoriasis by anti-IL17RA agents, this may confirm a true link between psoriasis inflammation and cardiovascular comobidities. Furthermore, this may hold a large potential for reducing the risk of cardiovascular comorbidities in subjects with psoriasis and other IL-17 driven inflammatory diseases.

8.7 Registration and publication

Basic information of this clinical trial will be registered in the global data registry, www.clinicaltrials.gov and https://eudract.ema.europa.eu before the first subject enters into the trial. The trial may also become registered in other online data registries.
The protocol will be registered with the Danish Data Protection Agency through the Central Denmark Region (Region Midt fællesanmeldelse) before initiation of the study.
Results of this clinical trial will be submitted for publication in a peer-reviewed scientific journal and/or submitted for publication at an international scientfic congress. Positive, negative, and inconclusive results will be published.
Results may also become reported in www.ClinicalTrials.gov and/or https://eudract.ema.europa.eu after clinical trial completion or premature termination.

8.8 Exposure to radiation

During FDG-PET/CT, the patients are exposed to ionising radiation in the amount of 4.8 mSv at each imaging procedure. In case of repeat scan after 16 weeks, this means that the subjects are exposed to a total amount of 9.6 mSv.
To minimize the exposure to ionizing radiation a low radiation dose protocol of 200 Mbq FDG is used. To avoid loss of data quality the low radiation dose protocol is combined with an extended PET acquisition time. This particular PET protocol implies a radiation dose of 3.8 mSv. Additionally, non-contrast low radiation dose CT is performed from just above the level of the aortic arch to the lower spleen level for attenuation correction and anatomical co-registration. The radiation dose associated with this part of the procedure is 1.0 mSv.
The total radiation dose for a subject completing the trial is thus: (2 x 3.8 mSv (PET) + 2 x 1.0 mSv (CT)) = 9.6 mSv. Background radiation in Denmark is approximately 3 mSV per year. The exposure to radiation in this study corresponds to 3-4 years of average background radiation. The additional cancer risk associated with the radiation exposure in this study is 0.048%. An additional cancer risk of 0.048% is equal to approximately 1 in 2080 chances. In a healthy individual younger than 50 years of age, the exposure of 9.6 mSV will increase the lifetime risk of dying from cancer from 25% to 25.048%.

There is no risk of deterministic effects in this study. The risk of stochastic effects is estimated to category IIb.

8.9 Benefit/risk assessment

There is an unmet medical need to reduce the increased risk of cardiovascular disease in patients with psoriasis. Cardiovascular disease caused by premature atherosclerosis is the cause of morbidity and decreased quality of life as well as increased mortality in patients with psoriasis. Due to the high prevalence of the disease this is relevant to a large number of patients. Brodalumab targets IL-17RA which has been shown as a key receptor in psoriasis patogenesis and a promising target in atherosclerosis.

Brodalumab has already demonstrated high efficacy and a favorable safety profile in the treatment of moderate-to-severe psoriasis in clinical studies. The drug is approved for the treatment of moderate-to-severe psoriasis by EMA and DMA.
In order to ensure appropriate treatment of the patients after they have completed the trial, the subjects will be treated at the investigator's discretion or referred to other physicians according to clinical practice and national treatment guidelines.

In patients undergoing FDG-PET/CT, it is well known that incidental focal lesions can be indicative of premalignant or malignant lesions. For instance, studies have shown that FDG-PET/CT reveals unexpected colonic FDG uptake in approximately 5% of patients and that a considerable number of these are diagnosed as premalignant or malignant.[47-49]
A high frequency of incidental PET findings have previously been shown in psoriasis patients.[50]
We found incidental focal colorectal FDG-uptake in one of 12 cases in our pilot study of aortic vascular inflammation in patients with moderate-to-severe psoriasis.[34] This particular case of asymptomatic colorectal cancer was diagnosed earlier than would have been the case if the patient had not undergone FDG-PET/CT. The cancer was curably removed by surgery.
In the current study, the low-dose FDG-PET/CT protocol will limit the area of interest to the thoracic and upper abdominal area.

The main risk in this study is associated with the exposure to radiation. A low radiation dose PET protocol and a limited non-enhanced CT protocol has been adopted to reduce the radiation dose to a minimum without sacrificing data quality.[51]

There is a risk that psoriasis may flare up during the wash-out period and during the study period for the patients included in the placebo group. Due to the relatively short duration of the study this is regarded as an acceptable risk and not associated with adverse outcomes. A similar period of treatment holiday may be seen during routine clinical practice when switching systemic treatments, in case of side-effects, travel, or when surgery must be performed.

During the PET procedure an intravenous access is needed which can cause minor bruising. The same risk applies to the laboratory blood test performed. A very small risk of infection is associated with intravenous procedures.

Accordingly, the optional punch biopsy is associated with a small risk of bleeding, infection, and scaring. The use of approximately 1 mL/per injection 2% lidocaine with epinephrine solution is associated with a small risk of systemic allergic reactions.

Some patients may experience claustrophobic sensations during the PET/CT procedure.

Efficacy and safety of brodalumab has been shown previously and the drug is approved for routine clinical use. Any risk associated with brodalumab is comparable to other biologic agents approved for the treatment of psoriasis. Participating patients will be candidates for systemic treatment.

In conclusion, the potential health-related benefits for the individual patient and for other psoriasis patients are considerable. Appropriate measures have been undertaken to reduce the risk for participating patients. The drug utilized is approved for clinical use and has documented high efficacy and a good safety profile. The current risk/benefit ratio is acceptable and supports the initiation of this study.

8.10 Ethical considerations

The study is conducted in compliance with the principles of the Declaration of Helsinki.
No children or other vulnerable subjects incapable of giving informed consent will be enrolled in this clinical trial. Furthermore, women who are pregnant, breastfeeding, or trying to become pregnant will not be enrolled in this clinical trial. Women of child-bearing potential have to agree to use a highly effective method of contraception to prevent pregnancy during the clinical trial. In addition, all female subjects of child-bearing potential will have a pregnancy test performed before treatment and study related procedures are commenced.
Only psoriasis patients will be enrolled, meaning that only patient who may benefit from the results obtained in this trial is participating.
Subjects are not reimbursed for participating in the trial, meaning that financial motivation will not lead to impaired judgment.

The risk of developing solid cancers follows a linear pattern with increasing dose although the age at which exposure takes place is highly relevant. A decline in radiosensitivity does take place with age, making young individuals more susceptible to radiation-induced malignancies. Although the malignancy risk for the population as a whole is 5 %/Sv, this is higher in children and considerably lower in older individuals.
The exposure to radiation restricts the age groups that may be enrolled to individuals > 40 years of age to reduce the stochastic risk of malignancies. Furthermore, by chosing this age-cutoff the study will include patients that may potentially benefit from incidental PET findings. Cardiovascular comorbidity and premature atherosclerotic disease associated with psoriasis are relevant for this age group. Younger indivuals more susceptible to radiation-induced malignancies and with low absolute risk of incidental malignant findings and cardiovascular disease are excluded from participation. Moreover, the typical mean age of

patients with moderate-to-severe psoriasis included in clinical trials is approximately 40-50 years.

Altogether, the risks associated with participating in this clinical trial are considered low and outweighed by the benefit of achieving high-quality scientific knowledge regarding the potential of reducing premature cardiovascular disease in patients with moderate-to-severe psoriasis.

In accordance with the current version of the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and Danish Executive Order number 695 of 12/06/2013, qualified medical personnel will be readily available to advise on trial-related medical questions. Medical monitoring will be performed by the GCP unit at Aarhus University throughout the trial.

In conclusion, the trial design chosen for this trial investigating the effect of brodalumab on aortic vascular inflammation and systemic inflammation is regarded as ethically justified and adherent with ethical requirements.

9 Trial objectives and endpoints

9.1 Trial objectives and endpoints

Objectives	Endpoints
Primary objective	**Primary endpoint**
To assess the change in aortic wall inflammation from baseline to week 16 in brodalumab treated psoriasis subjects compared to placebo.	• Change in the average of maximum TBR values (MeanTBR$_{max}$) of the entire aorta from baseline to week 16
Secondary objectives	**Secondary endpoint**
To assess the change in splenic inflammation from baseline to week 16 in brodalumab treated psoriasis subjects compared to placebo. To assess the change in aortic wall subsegment inflammation from baseline to week 16 in brodalumab treated psoriasis subjects compared to placebo. To assess whether changes in skin inflammation is associated with changes in aortic wall inflammation and/or changes in splenic inflammation.	• Change in the spleen-to-liver ratio (SLR) based on splenic and liver mean standardised uptake values (SUV$_{mean}$) • Change in the average of maximum TBR values (MeanTBR$_{max}$) of the ascending, aortic arch, descending, suprarenal, and infrarenal aorta from baseline to week 16 • Association between change in PASI and change in aortic wall MeanTBR$_{max}$ • Association between change in PASI and change in SLR
Additional secondary objectives	
To assess the change in subcutaneous adipose tissue inflammation from baseline to week 16 in	• Change in the average of maximum SUV values (MeanSUV$_{max}$) of the abdomial

brodalumab treated psoriasis subjects compared to placebo and whether this change is associated with changes in skin inflammation. To assess the change in soluble inflammatory biomarkers from baseline to week 16 in brodalumab treated psoriasis subjects compared to placebo. To assess whether the change in aortic wall inflammation and/or splenic inflammation is associated with psoriasis-specific genotypes. To assess the change in gene expression and cytokine expression in paired lesional and non-lesional psoriatic skin from baseline to week 16 in brodalumab treated psoriasis subjects compared to placebo.	subcutaneous adipose tissue from baseline to week 16 • Association between change in PASI and change in subcutaneous adipose tissue MeanSUV$_{max.}$ • Changes in acute phase proteins from baseline to week 16 • Correlation between changes in both aortic meanTBR$_{max}$ and SLR and prescence of HLA-B*08, HLA-C*06:02, HLA-B*27, HLA-B*38 and HLA-B*39 • Changes in gene expression and cytokine expression in skin samples from baseline to week 16 • Correlation with changes in mean aortic TBR$_{max}$ and SLR.

10 Trial design

10.1 Overall trial design

This is an investigator-initiated, single-center, randomized, double-blind (subjects, investigators, and nuclear medicine specialists and all staff involved in vascular imaging and analysis is blinded to group assignment) prospective, controlled study. Subjects are randomized and matched on sex and age (± 5 years) (stratified randomization).
Subjects with moderate-to-severe psoriasis are enrolled consecutively and randomly assigned to either active treatment with brodalumab or placebo during the treatment period. Subjects are entered into a pre-study washout period, if needed, wherein all active anti-psoriatic topical and systemic therapies are discontinued according to pre-specified time frames.
Psoriasis subjects are examined with FDG-PET/CT at baseline and again at end of study after 16 weeks of brodalumab treatment or placebo, respectively.
Baseline investigations include medical history, physical examination, and laboratory tests.

10.2 Number of subjects needed

Assuming a screening failure rate of 20%, approximately 62 patients will be screened and 50 patients will be included and randomly assigned to either brodalumab or placebo (1:1; 25 patients in each arm).
The statistical power calculation (section 14.1) includes the risk of drop-out before completion of the second FDG-PET/CT.

10.3 End of trial definition

A subject is considered to have completed the trial if they have completed all periods of the trial including the last FDG-PET/CT and end of study visit.
The end of the trial is defined as the date of the last visit of the last subject in the trial.

The Ethical committee and the Danish Medicines Agency will be notified ≤ 90 days after the end of the trial. Results will be posted in "EudraCT Results" ≤ 12 months after the end of the trial.

10.4 Record keeping, monitoring, and data handling

Case report forms
Data will be collected by means of electronic data capture in an eCRF (REDCap).
Personal data is protected according to the Act on Processing of Personal Data (lov om behandling af personoplysninger).

Source data
Source data should as a general rule be recorded in the subject's medical record or other defined document normally used at the trial site. Source data not normally collected as a routine part of the clinical practice may be entered directly in the eCRF.

Data entered directly in the eCRF are listed in appendix II.

The following data will as a minimum be added to the subject's medical record:

- Date(s) of conducting the informed consent process, including date of provision of subject information.
- A statement from the investigator to verify that the eligibility criteria are met.
- The fact that the subject is participating in a clinical trial in psoriasis including treatment arms of brodalumab or placebo for 16 weeks
- Other relevant medical information

Trial monitoring

The GCP unit at Aarhus University Hospital will be granted access to perform monitoring to confirm that the trial is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

In order to perform their role effectively, GCP unit staff involved in quality assurance and inspections will have direct access to source data, e.g. medical records, laboratory reports, appointment books, etc.
Upon request, inspectors from the Danish Medicines Agency will be granted the same access.

Data handling

Subject data should be entered into the CRF as soon as possible after each visit. Patient-reported data (data from questionnaires completed at the trial site) will be entered into the eCRF by the investigator.
Data will be stored for at least 5 years as required according to Danish legislation.

11 Trial population and withdrawal

11.1 Subject eligibility

Eligible patients must fulfill all eligibility criteria and be expected to comply with the protocol.

11.2 Inclusion criteria

1. Written informed consent obtained from the subject prior to performing any protocol-related procedures.
2. Age 40 and above.
3. Diagnosis of chronic plaque psoriasis confirmed by a dermatologist
4. PASI ≥ 10

11.3 Exclusion criteria

1. Non-Danish speaking
2. Known or suspected allergy or reaction to any component of the IMP formulation.
3. History of inflammatory bowel disease, arthritis (not including psoriatic arthritis), systemic lupus erythematosus, and active inflammatory skin diseases.
4. A history of malignancies within the past five years (excluding localized non-melanoma skin cancer).
5. Topical corticosteroid treatment (class III or stronger) and/or ultraviolet type B phototherapy within 2 weeks prior to randomization
6. Treatment with psoralen plus ultraviolet type A photochemotherapy, methotrexate, cyclosporine, acitretin, or fumaric acid esters within 4 weeks prior to randomization.
7. Treatment with adalimumab, etanercept, infliximab, cosentyx, or ixekizumab within 12 weeks, ustekinumab within 24 weeks, or other immunosuppressive or anti-inflammatory agents within 5 half-lives of the active substance prior to the FDG-PET/CT, respectively.
8. Scheduled surgery during the trial period (expect minor minimally invasive procedures).
9. Systemic infection or fever within 7 days prior to FDG-PET/CT.
10. Severe obesity (> 150 kg due to a PET/CT scanner limitation).

11. Presence of uncontrolled diabetes mellitus (HbA1c > 75 mmol/mol and/or blood sugar > 11.1 mmol/l and/or clinical judgment).
12. History of coagulation defects (clinical judgment).
13. Active or latent tuberculosis requiring treatment.
14. Positive hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb) or hepatitis C virus antibody (anti-HCV) serology at screening. Subjects with positive HBsAb may be randomised provided they are hepatitis B vaccinated and have negative HBsAg and HBcAb.
15. History of any known primary immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test at screening, or the subject taking antiretroviral medications as determined by medical history and/or subject's verbal report.
16. No history of varicella zoster infection and negative varicella antibody test (until varicella vaccination is completed).
17. History of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator.
18. History of intravenous drug use.
19. History of attempted suicide or is at significant risk of suicide.
20. Major surgery within the past 3 months.
21. Pregnancy or lactation (Women of childbearing potential must use a highly effective* form of birth control (confirmed by the investigator) throughout the trial and until 12 weeks after discontinuation of treatment with brodalumab.
22. Claustrophobia.
23. Reduced renal function (serum creatinine > 200 μmol/L or cr-EDTA clearance < 30 ml/min)
24. Any disorder, including but not limited to, cardiovascular, lung, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, immunological, psychiatric, or major physical impairment that is not stable, in the opinion of the investigator, and could:
    - Affect the safety of the subject throughout the trial.
    - Influence the findings of the trial or their interpretations.
    - Impede the subject's ability to complete the entire duration of trial.

* A highly effective method of birth control is defined as one which results in a low failure rate (less than 1% per year) such as bilateral tubal occlusion, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), sexual abstinence (when this is in line with the preferred and usual life style of the subject), vasectomised partner (given that the subject is monogamous). The subjects must have used the contraceptive method continuously for at least 1 month prior to the pregnancy test. A female is defined as not being of child bearing potential if she is postmenopausal (at least 12 months with no menses without an alternative medical cause prior to screening), or surgically sterile (hysterectomy, bilateral salpingectomy or bilateral oophorectomy).

11.4 Recruitment and informed consent procedures

Refer to Appendix IV for further details on recruitment and informed consent in Danish.

Prospective study subjects:

- Patients with moderate-to-severe psoriasis which is referred for treatment at Department of Dermatology, Aarhus University Hospital.
- Patients with moderate-to-severe psoriasis which is currently being treated at Department of Dermatology, Aarhus University Hospital.

Prospective study subjects are identified based on:

- Physician referral letters
- Medical records
- Patient lists

Typically, initial contact is made with a prospective subject during/before a scheduled routine appointment at the department of dermatology. The subjects will be invited for a formal informed consent dialogue by one of the investigators (KFH or LI) or another qualified HCP. Prospective subjects may be identified during the evaluation process of clinical physician referral letters. A recruitment letter (Appendix XI) may be sent to a prospective subject which is identified based on the referral letters. A contact may be performed by the investigators if the prospective subjects actively express a wish to learn more about the study. During this conversation, the prospective subject will be invited for a formal informed consent dialogue and a brief description of the trial will be provided. It is specifically emphasized that the dialogue and any further study participation is voluntarily and that standard clinical treatment is entirely possible at any stage.
Written study information will be provided when date, time, and place for a formal informed consent dialogue has been arranged.
The prospective subjects will be informed of the option to bring a family member or counselor at the formal dialogue.

Enviroment: The environment where the process of consent is conducted will enable a period where a private, confidential, and “safe” setting is afforded to facilitate a constructive dialogue between the prospective subject and the investigator(s) involved in obtaining consent. A physician’s office or an examination room in the clinical research department will typically be used.

Presentation of the Elements of Informed Consent: The required elements of informed consent will be presented and discussed with the prospective subject in a sequential manner utilizing the approved ”participant information” (appendix V) as a guide. The presentation will be structured to facilitate a dialogue with reinforcement and elaboration of important information (e.g., the risks of the research; radiation exposure, risk of flare). The investigator(s) involved in obtaining the subject’s consent will evaluate whether the process is achieving the goal which is obtainment of legally effective informed consent from the subject. Open-ended questions will be used in order to identify points of confusion which require clarification.

Use of a Delayed Consent Procedure: The amount of time allotted to the process of consent is individual and is decided at the subject's discretion. A 24 hour delay is suggested. If the individual is uncomfortable or anxious about participating in the study they will be instructed to take the written material home for further review and consideration before deciding whether or not to participate in the research.

Documentation of informed consent: The investigator who assumes responsibility for documentation of informed consent and the consenting subject should sign and date the informed consent form, preferably in each other's presence.

11.4.1 Information collected from the medical records

The following information is passed on from the clinical medical records as part of the screening process (evaluation of elegibility criteria):

- Age
- Sex
- Height and weight if available
- Severity of psoriasis and PsA
- Current treatment of psoriasis

The following information is collected from the clinical medical records after informed consent:

- Previous and current anti-psoriatic treatments
- Concomitant medication, procedures and diagnoses

11.5 Screening, screening failures, and randomisation

Trial participation begins once written informed consent is obtained. The screening evaluations to assess eligibility criteria may begin once informed consent is obtained. A master log of all consented subjects will be maintained at the trial site.
Screening failures are defined as subjects who consent to participate in the trial but are not subsequently randomly assigned to trial treatment. The following information is recorded in case of screening failure: demography, screening failure details, eligibility criteria, and any adverse events (AEs) and serious AEs (SAEs).

Individuals who do not meet the criteria for participation in this trial (screening failures) may not be re-screened. However, if the reason for screening failure is administrative and not due to the subject failing to meet the eligibility criteria, re-screening may be permitted.
Re-screening is permitted after a due washout period if screening failure is due to treatment with any of the substances listed in section 10.3.

11.6 Discontinuation

A subject may withdraw from trial or from treatment at any time (prior to FDG-PET/CT, first dose, or during treatment period) at his/her own request. A subject may be withdrawn at any time at the discretion of the investigator. Discontinued subjects will not be replaced if baseline FDG-PET/CT has been performed.

Assessments
Subjects who permanently discontinue treatment for any reason will be invited to attend an early termination visit for data to be collected. The investigator will review any AEs which will be followed-up according to clinical guidelines, if the subject agrees. In order to ensure appropriate treatment of the subjects after they have discontinued the trial, the subjects will be treated at the investigator's discretion or referred to other physicians according to clinical practice and national treatment guidelines.

Lost to follow-up
A subject will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the trial site. Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address and/or "e-boks"). These contact attempts should be documented in the subject's medical record.

11.7 Reimbursement

Subjects are not reimbursed for participating in the trial.

11.8 Insurance

Participating subjects are covered by The Patient Compensation Association as the study is conducted by authorized HCP's at a public healthcare hospital.

12 Treatments

12.1 Trial product description

Brodalumab is a recombinant fully human monoclonal immunoglobulin IgG2 antibody that binds with high affinity to human IL-17RA and blocks the biological activities of the pro

inflammatory cytokines IL-17A, IL-17F, IL-17A/F heterodimer and IL-25. Brodalumab is approved for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy. The trade name of brodalumab is Kyntheum and it is marketed by LEO Pharma A/S. Kyntheum is available as a 210 mg solution for injection. Further details is available from the product description (Appendix I).

Active substance:
Brodalumab (Kyntheum) 210 mg in a pre-filled syringe. The prefilled syringe is a single use, disposable system that is designed to administer the labeled dose of the medicinal product to the subcutaneous space during 1 injection.
Masking of the accessorised pre-filled syringes will be performed at the Central Denmark Region Hospital Pharmacy before delivery to the study site.

Placebo:
Placebo solution (1.5 mL Natriumklorid "Fresenius Kabi" 9 mg/ml solution)(Appendix XII) for injection in a pre-filled insulin-type syringe with a 30G-13 mm needle. The pre-filled injector is manufactered and masked at the Central Denmark Region Hospital Pharmacy before delivery to the study site.

12.2 Administration of investigational medicinal products

Brodalumab (Kyntheum) will be provided by the funding body (LEO Pharma A/S).

The first day of dosing is at visit 2 after completion of baseline FDG-PET/CT.

Experimental arm: Brodalumab
Eligible subjects will receive 210 mg of brodalumab administered by subcutaneous injection at Weeks 0, 1 and 2 followed by 210 mg every other week (EOW) thereafter.

Placebo comparator: Placebo
Eligible subjects will receive placebo doses administered by subcutaneous injection at Weeks 0, 1 and 2 followed by placebo EOW thereafter.

All subjects will be allowed to continue topical anti-psoriatic treatments as stated in section 12.4. Other systemic and topical anti-psoriatic treatments are not allowed.

The first dose of the investigational medicinal products is administered by a healthcare professional (HCP) at the trial site at visit 2. The investigational medicinal products will be administered by a qualified, unblinded HCP (see Section 11.3.1 for blinding details).
For the first IMP dosing visit, subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 15 minutes according to routine clinical practice. According to the investigators brochure (produktresume, appendix I) no monitoring is needed. However, the IMP is administered in the hospital setting where medication and equipment for acute life support is immediately available to physcians and nurses responsible for the treatment and monitoring of the subjects.

Subsequent doses will be administered as home-use by the subjects or the subject's caregiver. Prior to self-administration at home, the individual who will be administering the injections (i.e., the subject and/or the caregiver) will receive proper training in subcutaneous (SC) injection technique and on procedures to be followed in the event of an emergency during or following home-use of brodalumab. This training will be conducted by an unblinded HCP. Patients who do not want to self-inject may have the staff at the trial site administer all the injections at the trial site if applicable.

Subjects are instructed to contact the investigator/trial site in case of fever > 38°C within 72 hours prior to injection. In case a clinically significant infection is suspected the following actions can be taken at the investigator's discretion:

- Rescheduled administration of placebo/brodalumab
- Further work-up (e.g. laboratory tests) and concomitant treatment of infection

Patients are instructed to contact the investigator/trial site in case of fever > 38°C within 1 week prior to scheduled FDG-PET/CT. Rescheduling of FDG-PET/CT is at the investigator's discretion.

12.3 Treatment assignment

Subjects who have been found to comply with all the inclusion criteria and not to violate any of the exclusion criteria will be randomized at baseline (visit 2) to receive treatment with either brodalumab or placebo. Treatment assignment will be according to a computer generated randomization (REDCap, https://redcap.au.dk) in a 1:1 ratio. The method of randomization will be based on matched pairs design in which subjects will be matched on sex and age stratification (age decades; 40 – 49, 50 – 59, 60 – 69, 70 – 79, > 80).

12.3.1 Blinding

This is a double-blinded trial in which brodalumab and placebo are visually distinct from each other. The packaging and labelling of the products will contain no evidence of their identity.
Since brodalumab and placebo are visually distinct, the products will be handled and administered by a qualified, unblinded HCP at the site. A blinded study physician at the site will perform clinical assessment of PASI, IGA, BSA, nails, and joints at visit 2, 3, and 4. Subjects are not informed of the visual differences between placebo and brodalumab. Syringes are masked and with no posibility of identifying the content. The only visual difference will be minor color differences. Therefor, subjects will not be aware of the treatment received.

Subjects, investigators (except unblinded HCPs), and nuclear medicine specialists and all staff involved in vascular imaging and analysis is blinded to group assignment.

The trial site will maintain a written plan detailing which staff members are blinded/unblinded.

12.3.2 Emergency unblinding of individual subject treatment

Provisions are in place for 24 hour emergency unblinding of individual subject treatment. If emergency unblinding is required, the investigator can unblind a subject. Emergency envelopes of individual treatment allocation is maintained by the unblinded HCP's at the trial site. For a requester without access to the trial site (e.g., an HCP not involved in the trial), a 24 hour local contact number for the trial site is provided. The requester will provide the subject ID (Danish CPR number) to the staff who will reveal the individual treatment allocation. If necessary, the staff will facilitate contact to the investigators.

12.4 Background treatment (topical agents)

All subjects may use an additive-free, basic bland emollient twice daily and/or topical corticosteroid class II or weaker (danish classification of topical corticosteroids). Subjects are not allowed to start treatment with other prescription emollients including topical corticosteroids class III or stronger during the trial. Other topical and systemic anti-psoriatic treatments are not allowed.

12.5 Concomitant medication and procedures

Concomitant medication and procedures (including diagnosis, intervention, and start and stop date) are recorded in the subject's medical record and the eCRF. Investigators may prescribe concomitant medications or treatments to provide adequate supportive care as deemed necessary, except for medications listed in Section 11.6.
Concomitant medication for conditions other than psoriasis may be continued throughout the trial without any change in dosage whenever possible.

12.6 Prohibited medication and procedures

The following medications are prohibited during the trial from inclusion through week 16:

- Topical corticosteroid treatment (class III or stronger)
- Other topical treatments for psoriasis such as calcipotriol
- Ultraviolet type B phototherapy
- Psoralen plus ultraviolet type A photochemotherapy
- Methotrexate, cyclosporine, acitretin, and fumaric acid esters
- Adalimumab, etanercept, infliximab, cosentyx, ixekizumab, and ustekinumab
- Other immunosuppressive or anti-inflammatory agents including janus kinase inhibitors, interferon-gamma, or other biologics
- Immunoglobulin or blood products
- Systemic corticosteroids (nasal and inhaled corticosteroids are allowed)
- Allergen immunotherapy

- Live (attenuated) vaccine

12.7 Treatment logistics and accountability

12.7.1 Labelling and packaging of investigational medicinal products

The investigational medicinal products will be packaged in individually numbered kits, each containing 1 syringe (brodalumab 210 mg or placebo).
Primary and secondary packaging materials (syringe and outer carton, respectively) will be individually labelled. Labelling will not indicate whether the content of the syringe is brodalumab or placebo.

12.7.2 Storage of investigational medicinal products

Initial storage and relabeling of brodalumab are delegated to the Central Denmark Region Hospital Pharmacy. Products are subsequently delivered to the research facility at the Department of Dermatology, Aarhus University Hospital.
All investigational medicinal products will be stored in a secure and restricted area under the conditions specified on the label and remain in the re-labelled original container until dispensed.
The products will be stored at 2 to 8°C at the site. The temperature during storage will be monitored by a calibrated, stationary and continuously recording system.
A temperature log will be kept to document the storage within the right temperature interval.
Storage facilities will be checked at least every working day.
Subject's will be instructed to store Brodalumab for home-use at 2 to 8°C (refer to appendix I for details).

12.7.3 Drug accountability

An inventory (trial medication inventory log) will be kept of the investigational medicinal products administered/provided to each subject randomized in the trial. The trial medication inventory log will be available for inspection during monitoring visits.
Subjects will be provided with sharps bins for used syringes. Filled sharps bins will be returned to the trial site. Subjects will return trial kit cartons, and any unused products at next trial visit.

12.7.4 Trial product destruction

Unused investigational medicinal products as well as used syringes returned to the site will be shipped for destruction by the Department of Dermatology according to local approved procedures.

12.7.5 Treatment compliance

Subjects will record date and injection site for each administration in a log of drug administration; these data will then be transcribed into the eCRF by site staff at the next trial visit. Any non-compliance and the reason for it must be recorded in the eCRF.
If the treatment has been interrupted for any reason (e.g. clinically significant infection) the final visit can be postponed at the investigator's discretion with the number of weeks that the treatment was interrupted.
All used and unused syringes must be returned to the trial site.

12.8 Provision for subject care following trial completion

In order to ensure appropriate treatment of the subjects after they have completed the trial, subjects will be treated at the investigator's discretion or referred to other physicians according to clinical practice and national treatment guidelines. This also applies to subjects that dropout or terminates the study before completing all visits.

12.9 Reporting product complaints

Any defect with the brodalumab device will be reported to LEO Pharma A/S according to standard practice.

13 Trial schedule and assessments

13.1 Overview

Protocol approval (Danish Medicines Agency and Ethical Committee): by November 2017
First patient first visit: December 2017
Patient enrollment and investigational procedures: December 2017 – April 2019
Last patient last visit: April 2019
Data collection completion: May 2019
Data analysis and publication of results: Until January 2020

Evaluations to be done at each visit are shown in the schedule of procedures in Section 7. Refer to Section 10.1 for further details on the trial design.

During the course of the trial, subjects may need to be seen at unscheduled visits. The assessments to be performed at an unscheduled visit are left to the investigator's discretion. Assessment of psoriasis disease severity (PASI, IGA, BSA, nail count, and joint count) after randomization will be performed only by the blinded assessor.

13.2 Assessments performed only at screening/baseline

Assessments performed only at the screening and/or baseline visit include: assessment of

elegibility criteria, demographics, medical history, height, and weight. These are described in further detail below. Laboratory tests include hepatitis B, hepatitis C, HIV-1, HIV-2, T-spot, and serum pregnancy test. Varicella zoster antibody analysis may be relevant in some subjects. Procedures include chest X-ray.
A pre-treatment chart is completed before initiation of treatment according to national guidelines (Appendix III)

13.2.1 Demographics

The following demographic data will be recorded:
 Month and year of birth
 Sex
 Race: Asian, Black or African American, Middle East and North Africa, White, Other

13.2.2 Medical history

Relevant past and concurrent medical history must be recorded and includes:

- Psoriasis medical history: all past and current history including:
  - Duration of psoriasis in years
  - Severity of psoriasis
  - Previous psoriasis treatments
  - Psoriasis clinical manifestations (plaque, scalp, nails, genital/flexural)
  - Family history of psoriasis
  - Co-morbidities including psoriatic arthropathy*, obesity, diabetes mellitus, arterial hypertension, hypercholesterolemia, stroke, ischemic heart disease, and depresion

- Other medical and surgical history including concurrent diagnoses.

Relevant medical history includes also diseases which are specifically listed as exclusion criteria and diseases for which specific treatments are listed as exclusion criteria.

*Psoriatic arthropathy: history of formal psoriatic arthritis diagnosis or; pain, stiffness for >30 minutes in the morning / after prolonged inactivity. Improves with activity. Peripheral or with axial involvement – inflammatory back pain and stiffness that improve with activity. Night symptoms.

13.2.3 Height and weight

The subject's height must be measured (without shoes) and weight must be determined (in indoor clothing and without shoes).

13.3 Psoriasis efficacy assessments

13.3.1 Investigator assessments

13.3.1.1 Investigator's Global Assessment

The IGA is an instrument used in clinical trials to rate the severity of the subject's global psoriasis and is based on a 5-point scale ranging from 0 (clear) to 4 (severe).[52] The IGA score will be assessed according to the Schedule of procedures (Section 6). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit (static form of IGA). Assessment at screening is performed by a trained investigator. Assessment at baseline (visit 2) and follow-up (visit 3 and 4) will be performed by a blinded assessor only.

Investigator's Global Assessment

Score	**Disease severity**
0	Clear
1	Almost clear
2	Mild disease
3	Moderate disease
4	Severe disease

13.3.1.2 Psoriasis Area and Severity Index

The most widely used and best validated instrument for assessment of psoriasis disease severity is the *Psoriasis Area Severity Index* (PASI).[53-55] The PASI score rests on a physician's evaluation of the skin area involved, erythema, induration and scaling; and scores range from 0 to 72. Treatment response is assessed as PASI reduction in percentage. Even though there is no definite consensus, moderate-to-severe psoriasis is often defined as a PASI score ≥ 10.[56] Assessment at screening is performed by a trained investigator. Assessment at baseline (visit 2) and follow-up (visit 3 and 4) will be performed by a blinded assessor only.

Plaque characteristic	Rating score	Body region (and weighting factor)			
		Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Thickness					
Scaling					
Add together each of the 3 scores for each of the body regions to give 4 separate sub totals.					
Sub Totals		A1=	A2=	A3=	A4=
Multiply each sub total by amount of body surface area represented by that region i.e. A1 x 0.1 for head, A2 x 0.2 for upper limbs, A3 x 0.3 for trunk, A4 x 0.4 for lower limbs to give a value B1, B2, B3 and B4 for each body region respectively					
		A1 x 0.1 = B1	A2 x 0.2 = B2	A3 x 0.3 = B3	A4 x 0.4 = B4
		B1=	B2=	B3=	B4=
Degree of involvement as % for each body region affected; (score each region with score between 0–6)	0 = None 1 = 1–9% 2 = 10–29% 3 = 30–49% 4 = 50–69% 5 = 70–89% 6 = 90–100%				
For each body region multiply sub total B1, B2, B3 and B4 by the score (0–6) of the % of body region involved to give 4 subtotals C1, C2, C3 and C4					
		B1 x score = C1	B2 x score = C2	B3 x score = C3	B4 x score = C4
		C1=	C2=	C3=	C4=
The patient's PASI score is the sum of C1+C2+C3+C4				PASI=	

13.3.1.3 Body surface area involvement

The total BSA affected by psoriasis will be assessed.
Assessment at screening is performed by a trained investigator. Assessment at baseline (2) and follow-up (visit 3 and 4) will be performed by a blinded assessor only.

13.3.1.4 Quantitative nail assessment

The total number of nails affected by psoriasis will be assessed. The nails are assessed for both nail matrix psoriasis and nail bed psoriasis. Features of nail matrix psoriasis includes nail pitting, leukonychia, red spots in the lunula, and crumbling of the nail. Features of nail bed psoriasis includes onycholysis, oil drop (salmon patch), dyschromia, splinter hemorrhages, and nail bed hyperkeratosis.

Assessment at screening is performed by a trained investigator. Assessment at baseline (visit 2) and follow-up (visit 3 and 4) will be performed by a blinded assessor only.

13.3.1.5 Quantitative joint assessment

Joints are palpated for the purpose of determining if they are tender and/or swollen, the latter implying the presence of active synovitis, and both implying the presence of inflammation.[57] Joint swelling is defined as soft tissue swelling of the joint which is detectable along the joint margins. A synovial effusion invariably means that the joint is swollen. Fluctuance is a characteristic feature of swollen joints; neither bony enlargement nor deformity of the joint

constitutes “swelling”. Joint swelling may influence the range of joint motion, which can be useful to recognize the presence of swelling.[58]
Joint tenderness is defined as pain at rest that is induced by pressure at examination of some joints such as the metacarpophalangeal (MCP) and wrist joints. The assessor should use his/her thumb and index finger to exert pressure that is sufficient to cause whitening in the assessors nailbed, which is called the “rule of thumb”.[58]
The total number of swollen and the total number of tender joints will be recorded.

13.3.2 Subject assessments

13.3.2.1 Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a validated questionnaire with content specific to those with dermatology conditions. It consists of 10 items addressing the subject’s perception of the impact of their skin disease on different aspects of their quality of life (QoL) over the last week such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment.[59] Each item is scored on a 4 point Likert scale (0 = not at all /not relevant; 1 = a little; 2 = a lot; 3 = very much). The total score is the sum of the 10 items (0 to 30); a high score is indicative of a poor QoL. The DLQI will be completed according to the Schedule of procedures in Section 7 and at each self-injection during home-use of the investigational medicinal product. The DLQI is included in the appendix.

13.3.2.2 Psoriasis Symptom Inventory (PSI)

The Psoriasis Symptom Inventory (PSI) is an eight-item psoriasis-specific, patient-reported outcome measure used in assessing the severity of psoriasis symptoms.[60] The PSI has demonstrated excellent internal consistency, test–retest reliability, validity, and responsiveness in moderate to severe plaque psoriasis, based on a pooled analysis of data from a phase II clinical study (n = 198) to evaluate the efficacy of brodalumab in moderate to severe chronic plaque psoriasis.[61] The PSI consists of 8 items: itching, redness, scaling, burning, stinging, cracking, flaking, and pain. Patients were asked to complete the 24-hour and 7-day recall version of the PSI by rating the severity of each symptom on a 5- point categorical rating scale, ranging from not at all to very severe. The PSI can use a 24-hour recall and 7- day recall, and both versions have been found to yield comparable data.[60] A PSI total score is defined for each version as the sum of all 8 items and ranges from 0–32, with higher scores indicating greater severity.
The PSI will be completed according to the Schedule of procedures in Section 7 and at each self-injection during home-use of the investigational medicinal product. The PSI is included in the appendix.

13.3.2.3 Visual Analog Scale for joint pain

The pain is a unidimensional measure of pain intensity, which has been widely used in diverse adult populations, including those with rheumatic diseases.
A subjective assessment of the average joint pain over the last 3 days/nights is recorded by the subject on a visual analogue scale, where 0 is no pain and 100 is the worst imaginable joint pain.

13.4 Clinical and laboratory assessments

13.4.1 Physical examination

A thorough physical examination of the subject including whole body inspection of the skin and auscultation of heart, lungs and abdomen; palpation of the abdominal organs and basic neurological status will be performed at the screening visit.

Height, weight, hip circumference, blood pressure, and pulse will be assessed according to the Schedule of procedures in Section 6.

Blood pressure and pulse (vital signs) will be measured in supine position following at least 5 minutes rest.
If an abnormal vital sign at screening is considered by the investigator to be clinically significant, it will be up to the investigator's discretion if the subject should be randomized into the trial.
In case of abnormal findings, the vital sign measurement can be repeated approximately 15 minutes later with subjects resting in a supine position to verify the first measurement. Should the repeated measurement result in a normal value, the measurement must be repeated once more. If the third measurement verifies the second (normal) value, the first measurement will be considered as false. If the third measurement confirms the first measurement (abnormal) the second measurement will be considered as false. Only the last value measured and considered as correct will be recorded in the eCRF.

13.4.2 Pregnancy test

A urine pregnancy test (human chorionic gonadotropin; dipstick) will be performed at the trial site at screening prior to randomization in female subjects of child-bearing potential.

13.4.3 Laboratory testing

The following analyses will be performed at the Biochemical laboratory Aarhus University Hospital: Sodium, Potassium, Creatinine, C-reactive protein, Alkaline phosphatase, Alanine aminotransferase, Gamma glutamyl transferase, Cholesterol, LDL cholesterol, HDL cholesterol. Triglycerides, Glucose (non-fasting), Hba1c, Albumin, Hemoglobin, Leukocytes, Neutrophils, (neutrophils/total cells), Lymphocytes (lymphocytes/total cells) Monocytes (monocytes/total cells), Eosinophils (eosinophils/total cells), Basophils (basophils/total cells), Thrombocytes, Urinalysis (Protein, Glucose, Ketones, Occult blood, Leukocytes, Nitrite).

Analysis of hepatitis serology and HIV 1+2 will be performed according to institutional protocols. Analysis of varicella zoster antibodies will be performed in case of no history of previous varicella zoster infection. These tests are standard procedures before commencing treatment with biologic agents.
A sample of 4 mL blood in an EDTA-tube is collected for storage at visit 1 (screening) and visit 3 (week 6). Plasma is separated from erythrocytes by centrifugation and stored at -150°C for later analysis of inflammatory markers.

13.4.4 Procedures

Chest X-ray will be performed at a collaborating radiology imaging facility as part of the screening. If a chest X-ray result is abnormal and considered by the investigator to be clinically significant, it will be up to the investigator's discretion if the subject should be enrolled into the trial.
The procedure may be omitted if a chest x-ray has been performed within 6 months before screening and the result is accessible and normal.

Punch biopsies will be performed as optional procedures. A supplementary informed consent form must be signed. A lesional and a non-lesional 4 mm punch biopsy will be performed in local anesthesia (approximately 1 mL/per injection 2% lidocaine with epinephrine solution) according to institutional guidelines. The punch biopsies will be performed at baseline and at visit 3 / 6 Weeks. Subjects will have the option to accept or decline punch biopsies. The acceptance or rejection of this procedure does not otherwise affect the eligibility of subjects. Punch biopsies will be snap frozen in liquid nitrogen and stored at -150°C for later analysis of IL-17 downstream pro-inflammatory marker genes (e.g. Nfkbiz, CCL20, Defb4) by qPCR.

13.4.5 Research biobank

Samples of plasma (4 mL) are collected for storage in a research biobank at visit 1 (screening) and visit 3 (week 6). Optional skin punch biopsies are collected at baseline and visit 3 (week 6).
Purpose of the research biobank is to store the biological material safely until analysis of inflammatory markers can be performed in all samples.
Termination of the research biobank: January 2020.
Any remaining biological materials after this date will be anonymized or destroyed.

13.5 FDG-PET/CT assessments

13.5.1 Patient preparation

FDG-PET/CT will be performed after an overnight fast using a combined PET/CT scanner (Siemens Biograph 64 PET/CT (Siemens, Germany)). FDG will be administered intravenously (approximately 200 MBq) and patients will rest comfortably for approximately 90 to 120 min in a well-tempered environment.

13.5.2 FDG dose and circulation time

For arterial imaging with PET, longer delays between FDG injection and PET imaging than those used for oncology are recommended to allow sufficient FDG accumulation in the arterial wall and to reduce the intensity of FDG signal in the blood. The FDG circulation time is critical as optimal contrast between the target (plaque, arterial wall) and the background (blood) is essential to ensure accurate quantification of plaque FDG uptake. Based on previous results and current recommendations,[45] **the acquisition of PET images is performed 2 hours after injection**. This imaging delay represents the best compromise between a low background signal in blood and an acceptable duration of the PET study for patients.
To obtain a radiation dose as low as reasonably achievable, a **200 MBq protocol** has been adopted. It has previously been shown that low-radiation-dose protocols can be used in arterial FDG-PET imaging without undue degradation of either image quality or lesion quantification.[62]

13.5.3 Pre-scan fasting glucose

Fasting glucose will be assessed before FDG-PET/CT. Vascular imaging should ideally be performed in patients with prescan glucose levels lower than approximately 7.0 – 7.2 mmol/l). In patients in whom these blood glucose levels cannot be achieved, correction of the vascular FDG uptake according to the EANM recommendations for oncological PET imaging will be considered at the discretion of the nuclear medicine expert investigator.

13.5.4 Image acquisition

A low dose CT from the skull base level to the lower spleen level will be performed first for attenuation correction and anatomical co-registration. Imaging of the entire aorta, spleen and truncal adipose tissue will be performed next over 15–30 min (1 or 2 bed positions) acquisition time depending on the patient's anatomy.

13.5.5 Reconstruction protocol

Reconstruction of attenuation-corrected images will be done using an ordered subset expectation maximization algorithm with point-spread function (PSF) and time-of-flight (three iterations, 24 subsets, matrix size 192 x 192, 4-mm Gaussian postprocessing filter).

13.5.6 Quantification of radiotracer uptake in target tissue

PET and CT data will be fused and analysed with PMOD v3.703 (PMOD Technologies, Zurich, Switzerland). CT and PET images will be reviewed for quality and the images are manually co-

registered to ensure optimal anatomical correlation. Image analysis will be performed in accordance with recent nuclear medicine imaging guidelines by one expert observer. For the aorta, measurements are made every 3 mm, starting above the aortic valve level and continuing to the aortic bifurcation, approximately 200 slices per patient. Measurements are made in the axial planes by drawing a region of interest (ROI) containing the arterial wall and the lumen in each slice. The maximum standardized uptake values (SUVmax) of FDG within each ROI are recorded as a time- and dose-corrected tissue radioactivity divided by body weight.
Blood SUVmean are measured by drawing small ROIs in the superior vena cava and then averaged to approach one single most accurate value for the circulating blood-pool signal in each individual. The target-to-background ratio (TBR) will be calculated from the ratio of the SUV of the artery compared with background venous activity. Aortic FDG uptake will be assessed using the average TBRmax. Subcutaneous adipose tissue inflammation will be assessed and compared as SUVmax and TBR based on SUVmax. Targets are truncal subcutaneous adipose tissue localized beneath psoriatic plaques as indicated by the investigator.
Splenic inflammation is measured using mean standardised uptake values (SUV_{mean}) and the spleen-to-liver ratio (SLR) in accordance with current recommendations and previously published methodology [63-66]. Spleen volume of interst (VOI)s are drawn on five adjacent axial slices covering the central part of the organ, whereas liver VOIs are drawn on six adjacent axial slices in the right lobe.

14 Adverse events

14.1 Collection and reporting of adverse events

AEs[1] will be be collected from time of first dosing of IMP until completion of the clinical trial. At all visits, the subject will be asked a non-leading question by the investigator about AEs, for example: “How have you felt since I saw you last?” No specific symptoms will be asked for. It is important that the investigator also observes the subject for any changes not reported by the subject and records these changes.
SUSARs (Suspected, Unexpected Serious Adverse Reactions[2]) will be immediately reported directly to the Danish Medicines Agency in accordance with Danish legislation.
All SAEs[3] (Serious Adverse Events) and applicable AEs will be recorded in the medical record and the eCRF.
Section 4.8 in the Product Information (appendix I) serves as reference for determining the relevance of events/reactions.
It is the responsibility of the investigators to forward an annual safety report including a list of SAEs to the Ethical committee and the Danish Medicines Agency.
All serious adverse reactions (SARs) from the entire trial must appear from the annual report on the trial subjects’ safety. This includes expected as well as unexpected serious adverse reactions (SARs and SUSARs)
All important adverse events from the trial must appear from the final reporting of trial results in the EudraCT database in accordance with the EU guideline 2008/C168/02.

[1] Adverse event: Medical occurrence temporally associated with the use of a medicinal product, but not necessarily causally related

[2]Adverse reaction: All untoward and unintended responses to an investigational medicinal product related to any dose administered.

- The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.
- The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.
- An untoward and unintended response to a non-IMP which does not result from a possible interaction with an IMP is, by definition, not a SUSAR

'Serious' adverse reaction:
Regarding the criterion of 'seriousness', reference is made to footnote 3.

[3]An SAE is any untoward medical occurrence that

- results in death.
- is life-threatening.
- requires inpatient hospitalisation or prolongation of existing hospitalisation. (Planned hospitalisation or planned prolonged hospitalisation do not fulfill the criteria for being an SAE but should be documented in the subject's medical record).
- results in persistent or significant disability/incapacity.
- is a congenital anomaly/birth defect.
- is a medically important condition. Events that may not be immediately lifethreatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples are intensive treatment in an emergency room or at home for allergic broncospasm, blood dyscrasias and convulsions that do not result in hospitalization, development of drug dependency or drug abuse.

15 Statistical methods

15.1 Sample size

Derived from our investigations of vascular inflammation in psoriasis patients and control subjects, we expect a mean aortic TBR_{max} of 2.4 with a standard deviation of 0.35 in the psoriasis subjects. After succesful treatment with biologic agents, we expect the $MeanTBR_{max}$ in the psoriasis subjects to be reduced to 2.1 with SD 0.35. Based on these assumptions and an alpha-level of 0.05 we calculate that 22 psoriasis subjects in each study arm will provide a power of 80% to detect a difference between the groups. By choosing a sample size of 25 psoriasis subjects we allow for a dropout of 3 subjects at follow-up without reducing power significantly.

15.2 Trial analysis sets

A per protocol analysis set will be used as the main efficacy measure for the analysis of the endpoints at week 16.
The per protocol analysis set will be defined by excluding subjects for whom any of the following conditions apply:

- major protocol violations (e.g. did not receive treatment with investigational medicinal product)
- are known to have initiated prohibited medicine (section 11.6) during the trial
- follow-up FDG-PET/CT not completed

15.3 Statistical analysis

15.3.1 Disposition of subjects

For all randomised subjects the reasons for leaving the trial in the follow-up period will be presented by last visit attended and last week completed for each group, respectively.

15.3.2 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomised subjects. The presentations will be by treatment group.
Demographics include age, sex, and race. Other baseline characteristics include height, weight, body mass index, waist circumference, duration of psoriasis, PASI, nail and joint involvement, DLQI, concurrent diagnoses, concomitant medication, and previous psoriasis treatments.

15.3.3 Treatment efficacy

Efficacy of brodalumab on skin, nails, and joints compared to placebo will be shown as reduction in PASI, IGA, DLQI, VAS, joint count, and nail count at week 16 for both groups.

15.4 Analysis of endpoints

15.4.1 Analysis of primary endpoints

The primary endpoint, change in the average of maximum TBR values (MeanTBR$_{max}$) of the entire aorta from baseline to week 16, will be analysed for the per protocol analysis set. The endpoint will be analysed using a repeated measurements model.
Estimates and 95% confidence intervals (CIs) or standard deviations (SDs) for the change in meanTBR$_{max}$ and treatment differences will be presented. Values for the entire aorta and aortic subsegments will be presented. The difference in efficacy between treatment groups will be analysed. The null hypothesis of no difference in change in meanTBR$_{max}$ between

brodalumab and placebo will be tested against the two-sided alternative that there is a difference.
If applicable, a supportive multivariate analysis will be performed to test the effect of the continuous covariates age, body mass index, statin treatment and categorical variables gender and smoking status on the difference in vascular FDG uptake at week 16.

15.4.2 Analysis of secondary endpoints

The 4 secondary efficacy endpoints evaluate the impact of 16 weeks of treatment on (I) change in SLR, (II) change in the average of maximum TBR values ($MeanTBR_{max}$) of each aortic subsegment (ascending, aortic arch, descending, suprarenal, and infrarenal aorta), (III) association between change in PASI and change in aortic wall FDG-uptake, (IV) association between change in PASI and change in SLR.
These endpoints will be evaluated by testing the hypothesis of no difference between brodalumab and placebo. The endpoints will be analysed and presented for the per protocol analysis set.
The change from baseline to Week 16 in SLR and aortic subsegment FDG-uptake are continuous endpoints and will be analysed using a repeated measurements model.
If applicable, a supportive multivariate analysis will be performed as described in section 12.4.1.

15.4.3 Analysis of other endpoints

Change in acute phase proteins at week 16 between groups and change in abdominal subcutaneous adipose tissue FDG-uptake will be analysed using a repeated measures model. Changes in cytokine expression and gene expression in optional skin samples will be analysed using a repeated measures model. Association between change in PASI and change in subcutaneous adipose tissue as well as the association between change in TBR/SLR and psoriasis-specific genotypes will be computed using applicable correlation coefficients.

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17 Appendix

Please find the following appendices enclosed:

Appendix I:	Investigators brochure (Kyntheum produktresume in danish)
Appendix II:	List of source data captured in the eCRF
Appendix III:	Screening chart
Appendix IV:	Protokolresume in danish
Appendix V:	Deltagerinformation in danish
Appendix VI:	Informed consent
Appendix VII:	DLQI
Appendix VIII:	VAS score
Appendix IX:	Subject Logbog
Appendix X:	PSI – Patient symptomliste
Appendix XI:	Recruitment letter (rekrutteringsbrev)
Appendix XII:	Produktresume in danish Natriumklorid "Fresenius Kabi" 9 mg/ml

Deltagerformation og samtykkeerklæring vedrørende deltagelse i et sundhedsvidenskabeligt forsøg.

Effekten af brodalumab sammenlignet med placebo på inflammation i hovedpulsåren hos patienter med moderat til svær psoriasis

Originale titel:

Effect of brodalumab compared to placebo on vascular inflammation in moderate-to-severe psoriasis

A randomised, double-blind, placebo-controlled, trial to evaluate the efficacy of brodalumab monotherapy on vascular and systemic inflammation by 18F-FDG-PET/CT in subjects with moderate-to-severe plaque-type psoriasis who are candidates for systemic therapy

Projekt nr. 2017-003697-14
Godkendt den

Projekt ansvarlige:
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Vil du deltage i et sundhedsvidenskabeligt forsøg, som skal belyse, om det biologiske behandlingsmiddel "brodalumab" (Kyntheum) kan mindske betændelsesgraden i hovedpulsåren og kroppen generelt hos psoriasis patienter?

I det følgende er beskrevet, hvad forsøget går ud på, og hvad det indebærer. Først når du er blevet informeret af en læge og har læst og forstået det følgende, skal du afgøre, om du vil deltage.

Du har krav på betænkningstid og på at få mundtlig information sammen med en bisidder, hvis du ønsker det. Vi beder dig endvidere om at læse den vedlagte brochure "*Før du beslutter dig*", som er udgivet af Den Nationale Videnskabsetiske Komité.

Din deltagelse er frivillig, og du kan altid fortryde og vælge at udgå af projektet, uden at det får konsekvenser for din videre behandling. Du vil fortsat blive undersøgt, behandlet, og kontrolleret efter afdelingens sædvanlige procedurer.

Dette videnskabelige forsøg foregår i et samarbejde mellem Hud- og Kønssygdomme på Aarhus Universitetshospital og Nuklearmedicin og PET, Aarhus Universitetshospital.
I perioden fra december 2017 til og med marts 2019 vil vi gerne undersøge 50 patienter med moderat-til-svær psoriasis – hver patient vil blive fulgt gennem en 16 ugers periode. Halvdelen vil modtage behandling med brodalumab. Den anden halvdel vil modtage behandling med et blindpræparat (placebo).

Den projekt ansvarlige er afdelingslæge, PhD Anne Bregnhøj, og de øvrige projektansvarlige er professor Lars Iversen på Hud- og Kønssygdomme, Aarhus Universitetshospital, afdelingslæge, PhD Trine Høgsberg på Hud- og Kønssygdomme, Aarhus Universitetshospital og overlæge, PhD Lars Gormsen på Nuklearmedicin og PET, Aarhus Universitetshospital.

Det videnskabelige forsøg vil bidrage med viden om den forøgede risiko for hjertekarsygdom, der knytter sig til psoriasis, og kan være med til at afklare, om effektiv behandling af psoriasis kan bremse de processer i kroppen, der fører til fremskyndet åreforkalkningssygdom.

Baggrund

Psoriasis er en kronisk inflammatorisk (betændelses) sygdom. Ved et psoriasis udbrud er der inflammation i huden, som er en betændelsesreaktion uden bakterier. Inflammationen i huden, som resulterer i psoriasis, er en kompliceret proces, som involver både kroppens immunforsvar og cellerne i huden.

Igennem de senere år har forskning vist, at mennesker med psoriasis har større risiko for at få sukkersyge, forhøjet blodtryk, forhøjet kolesterol og fedme. Samtidig ved man, at disse sygdomme giver en større risiko for at få hjertekarsygdomme med blodpropper i hjertet eller hjernen. Desuden har forskningsresultater vist, at psoriasis i sig selv er forbundet med en forøget risiko for hjertekarsygdomme og hjertedød uafhængigt af de klassiske risikofaktorer for hjertekarsygdom. Denne sammenhæng menes at skyldes, at åreforkalkning også er en tilstand, hvor betændelseslignende reaktioner spiller en stor rolle. Der er mange fællestræk mellem betændelsesreaktionen ved psoriasis, og den der foregår i blodkar med åreforkalkning. Betændelsesreaktionen ved psoriasis forårsager formentlig en forøget grad af betændelse i blodkarrene, hvilket fører til en øget risiko for hjertekarsygdomme.
Denne sammenhæng mellem psoriasis i huden og sygdomme i kroppens indre organer, har medført, at man nu betragter psoriasis som en systemisk inflammatorisk sygdom, der kan påvirke hele kroppen.
Et begrænset antal studier har indikeret, at man kan bremse den fremskyndende åreforkalkningsproces ved at behandle moderat til svær psoriasis effektivt, men man ved endnu ikke meget om denne sammenhæng, og man ved ikke om moderne biologiske præparater kan nedbringe graden af betændelse i de store blodkar.
Studiet er vigtigt for at afklare, om effektiv behandling af psoriasis med biologiske præparater som brodalumab (Kyntheum) kan nedbringe inflammationsgraden i karsystemet og kroppen generelt, og dermed mindske den fremskyndede åreforkalkningsproces.

Formål

I dette projekt vil vi undersøge, om behandling med det biologiske præparat brodalumab (Kyntheum) kan nedbringe graden af betændelse i hovedpulsåren, betændelse generelt i kroppen og betændelse i fedtvævet hos mennesker med moderat-til-svær psoriasis.

Metode:

Til at måle inflammation i kroppen anvendes en såkaldt PET/CT skanning. Ved denne undersøgelse får forsøgspersonen indsprøjtet en lille mængde radioaktivt mærket sukkerstof i blodåren, som optages særligt i inflammatoriske (betændelseslignende) celler. PET/CT-skanneren kan derefter måle radioaktiviteten i kroppen med stor følsomhed og derved påvise, hvor og i hvor høj grad der er inflammation.

Du vil blive skannet ved starten af studiet og igen ved afslutningen af din deltagelse efter 16 uger. Skanningsresultaterne fra de første skanninger vil herefter kunne sammenlignes med de afsluttende skanninger, for at afgøre, om præparatet brodalumab kan mindske graden af betændelse sammenlignet med placebo.

Du vil blive tildelt enten aktiv behandling med brodalumab eller behandling med placebo efter et tilfældighedsprincip. Det personale, der står for skanningerne på Nuklarmedicin og

PET, vil ikke vide, hvilken gruppe du tilhører. Når hele forsøget er afsluttet, vil du kunne få at vide, hvilken behandling du har fået. Du kan få oplyst om dine skanninger har vist tegn på sygdom efter ca. en uge.

Det aktive præparat, der anvendes, er "brodalumab", handelsnavn i Europa "Kyntheum".
Brodalumab tilhører gruppen af biologisk medicin godkendt til behandling af moderat til svær psoriasis. Der er tale om et antistof, der blokerer de signalveje i immunsystemet, som er opreguleret i for høj grad hos mennesker med bl.a. psoriasis. Præparatet justerer med andre ord på den ubalance i immunsystemet, der giver anledning til psoriasis. Undersøgelser har vist, at brodalumab er sikkert at bruge, og det har en hurtigt indsættende og effektiv virkning på psoriasis. Brodalumab (Kyntheum) anvendes i sin standarddosering, som er 210 mg.

Hvis du får lysbehandling eller tablet behandling for din psoriasis og gerne vil deltage, kan det være nødvendigt at stoppe din behandling i 2-4 uger forud for PET/CT skanningen. Hvis du får indsprøjtninger med biologiske lægemidler, kan behandlingspausen være længere. Inden du beslutter, om du vil deltage i projektet, vil vi oplyse dig om, hvor lang behandlingspause der er behov for i dit tilfælde. Umiddelbart efter den afsluttende PET/CT-skanning vil der blive lavet en behandlingsplan for den videre behandling af din psoriasis i forløbet efter forskningsundersøgelsen. Den videre behandling vil følge de almindelige retningslinjer for behandling af psoriasis og bl.a. afhænge af sværhedsgraden af din hudsygdom og om der er tegn på psoriasisgigt.

Brodalumab (Kyntheum) er godkendt til behandling af moderat til svær plaque psoriasis. Standardbehandlingen af psoriasis afhænger af en række forhold, herunder sværhedsgrad af sygdommen, tilstedeværelse af eventuelle følgesygdomme og tidligere forsøgte behandlinger. Såfremt du ikke ønsker at deltage i studiet, vil du have mulighed for at modtage behandling i henhold til de almindelige retningslinjer for behandling af psoriasis.

Graviditet og amning
Hvis du er gravid eller ammer, har mistanke om, at du er gravid, eller planlægger at blive gravid, har du ikke mulighed for at deltage i forsøget. Brodalumab (Kyntheum) er ikke blevet testet hos gravide kvinder, og det vides ikke, om lægemidlet kan skade dit ufødte barn. Du bør derfor undgå brugen af Kyntheum under graviditeten. Endvidere bør PET/CT skanninger undgåes under graviditeten grundet udsættelse for stråling. Hvis du er en kvinde i den fødedygtige alder, skal du undgå at blive gravid, og du skal bruge sikker prævention, mens du er i behandling med forsøgslægemidlet og i mindst 12 uger efter den sidste dosis forsøgslægemiddel.
Følgende svangerskabsforebyggende midler anses som sikker prævention: Spiral eller hormonel prævention (p-piller, implantat, transdermal depotplastre, vaginalring eller depotinjektion). Sterile eller ikke fertile forsøgsdeltagere er fritaget for kravet om brug af prævention. For at betragtes som steril eller ikke fertil, må man almindeligvis være kirurgisk steriliseret eller være postmenopausal, defineret som udebleven menstruation i

mindst 12 måneder før studie indrullering. Kirurgisk sterilisation af fast mandlig partner kan være tilstrækkelig prævention.
Det vides ikke, om brodalumab udskilles i modermælken. Du har ikke mulighed for at deltage i studiet, hvis du ammer eller planlægger at amme.

Plan for forsøget:
Der indgår 4 besøg på hudafdelingen, hvoraf det første besøg består af en konsultation og undersøgelse samt screening for, om du opfylder kriterierne for at deltage i forsøget. Selve behandlingsperioden strækker sig over 16 uger. De resterende 3 besøg på hudafdelingen vil blive i løbet af denne periode; ved påbegyndelse af behandlingen, efter 6 ugers behandling og efter 16 ugers behandling. Der indgår 2 besøg på Nuklearmedicin og PET, hvor du får foretaget PET/CT-skanningerne. De 2 besøg på Nuklearmedicin og PET vil så vidt muligt blive planlagt til samme dag som 2 af besøgene på hudafdelingen.

Hvis du deltager i den videnskabelige undersøgelse, vil den første del af forløbet minde meget om det almindelige program for forundersøgelse til biologisk behandling af psoriasis.

- Som en almindelig del af en ambulant konsultation for psoriasis på Hud- og Kønssygdomme vil du få en lægelig samtale og undersøgelse.
- Du vil også få taget en blodprøve fra armen. Blodprøven bliver taget af en erfaren medarbejder på afdelingens laboratorium. Blodprøven består af 2-5 blodprøveglas a 3-5ml. Blodet skal bruges til rutine undersøgelser af infektionstal, væsketal, levertal, blodsukker, kolesteroltal og screening for leverbetændelse, HIV og tuberkulose. Herudover vil der blive analyseret for enkelte markører på systemisk betændelse (inflammation). Når blodprøverne er analyseret, indgår resultaterne i din patientjournal og i den database, der anvendes i forskningsprojektet. En mindre del af blodet vil blive frosset ned og opbevaret i en periode i en fryser godkendt til formålet, idet nogle analyser ikke kan foretages med det samme på den friske blodprøve, men vil blive udført senere, når alle blodprøver fra alle forsøgsdeltagere foreligger. Se ”biologisk materiale” for nærmere oplysninger.
- Der tages eventuelt en hudprøve fra et område med psoriasis og fra et raskt hudområde. Det drejer sig om stansebiopsier der er 4 mm i diameter og ca 4-5 mm i dybden. Prøverne tages inden påbegyndelse af projektmedicin og igen efter 6 uger. Det er frivilligt, om du vil indgå i denne del af studiet. Hvis du ikke ønsker at donere vævsprøver, kan du fortsat deltage i resten af forskningsundersøgelsen.
- Du vil blive henvist til at få foretaget et røntgen billede af lungerne, medmindre du for nyligt har fået foretaget en sådan undersøgelse. Denne undersøgelse er ligeledes standard inden påbegyndelse af biologisk behandling af psoriasis.
- Til forskningsprojektet skal vi bruge oplysninger om din sygdomshistorie, medicinske behandling, andre sygdomme, højde, vægt, taljemål, blodtryk, nyretal, infektionstal, kolesterol, blodsukker, samt tobak og alkohol forbrug. Resultaterne af din undersøgelse og oplysninger vil i anonymiseret form indgå i sammenligningen af de to behandlingsgrupper i forsøget.

- Kvinder i den fertile alder skal anvende sikker kontraception (beskyttelse) under behandlingen og i mindst 12 uger efter behandlingen.
- Når de forskellige forundersøgelser er gennemført og resultaterne foreligger, vil du få besked om hvad undersøgelserne har vist, og om du kan fortsætte i studiet eller om prøveresultaterne evt. har givet anledning til at foretage yderligere undersøgelser (f.eks. ved unormale blodprøver eller lignende).
- Hvis forundersøgelserne er upåfaldende, vil du blive henvist til PET/CT-skanning, og du vil få en tid umiddelbart efter i forskningsambulatoriet på Hud- og Kønssygdomme. Du vil her modtage den første behandling med projektmedicin (brodalumab (Kyntheum) eller placebo) og få yderligere medicin med hjem til hjemmebehandling.
- Du vil ikke kunne se på medicinen om indholdet er det aktive stof eller placebo.
- Du vil blive lært op i at injicere dig selv med medicinen. Injektionen minder meget om den måde, hvorpå sukkersyge-patienter injicerer sig selv med insulin.
- Oplæring i hjemmebehandling og forholdene omkring hjemmebehandling følger de normale retningslinjer og er standard ved de fleste biologiske behandlinger af psoriasis.
- Du vil få en injektion på Hud- og Kønssygdomme ved kontrollen umiddelbart efter PET/CT-skanningen. Herefter vil du derhjemme skulle injicere dig efter 1 og 2 uger, og derefter fast hver 2. uge.
- Du vil få en tid til kontrol i forskningsambulatoriet efter 6 uger og igen efter 16 uger.
- Den afsluttende PET/CT-skanning vil ligeledes blive udført efter 16 uger.
- I forbindelse med den afsluttende kontrol i forskningsambulatoriet aftales, hvordan den videre behandling af din psoriasis skal forløbe. Efter aftale med dig planlægges anden behandling evt. med det samme.
- Umiddelbart efter at din deltagelse i studiet er slut, vil du kunne få svar på om PET/CT-skanningerne har vist tegn til anden sygdom. Der vil typisk gå ca. en uge fra den sidste undersøgelse er udført, til skanningerne er blevet gennemgået for tegn på anden sygdom. Ved mistanke om alvorlig sygdom som eksempelvis kræft vil du dog blive orienteret indenfor ca. en uge efter den første PET/CT-skanning.

I dette studie afprøves ikke nye lægemidler, idet brodalumab (Kyntheum) er en godkendt behandling til psoriasis. Der undersøges dog for nye effekter af dette præparat i forhold til at mindske graden af betændelse i karsystemet og kroppen generelt. Der indgår som anført tilfældig fordeling (randomisering) og et blindpræparat (placebo).

PET/CT-skanning er en almindelig anerkendt undersøgelse metode, som anvendes rutinemæssigt på PET-Centret, Nuklearmedicinsk afd., Aarhus Universitetshospital. PET/CT-skanninger anvendes normalt til undersøgelse for bl.a. infektionssygdomme, kræftsygdomme og andre inflammatoriske sygdomme.

Biologisk materiale:

Da ikke alle analyser straks kan udføres oprettes en forskningsbiobank.

- Der udtages ca. 4 ml blod ved den almindelige blodprøvetagning ved screeningsbesøget og igen efter 6 uger. Disse 4 ml blod nedfryses i en fryser, der er placeret i et aflåst rum i forskningsfaciliteterne tilknyttet Hud og Kønssygdomme.
- Herudover indgår eventuelt en hudprøve fra et område med psoriasis og fra et raskt hudområde. Det drejer sig om stansebiopsier der er 4 mm i diameter og ca 4-5 mm i dybden. Prøverne tages inden påbegyndelse af projektmedicin og igen efter 6 uger. Det er frivilligt, om du vil indgå i denne del af studiet. Hvis du ikke ønsker at donere vævsprøver, kan du fortsat deltage i resten af forskningsundersøgelsen. Vævsprøverne nedfryses i afdelingens forskningsfaciliteter og analyseres for signalmolekyer som er involveret i sygdomsmekanismen ved psoriasis. Disse signalmolekyler antages at blive blokeret af Kyntheum (brodalumab).
- Ved blodprøvetagningen er der risiko for let ubehag ved selve indstikket, ligesom der er en risiko for et lille blår mærke ved indstiksstedet. Enkelte personer kan føle alment ubehag ved at få taget blodprøver.
- Ved de frivillige hudbiopsier kan der være kortvarigt let til moderat svie i huden ved lokalbedøvelse af området. Selve udtagningen af hudbiopsierne er som regel smertefrit. Efterfølgende er der risiko for let blødning fra området og en lille risiko for infektion. Du vil i forbindelse med hudbiopsierne få forklaret tegnene på infektion og hvordan du skal forholde dig ved blødning fra området eller ved infektionstegn. Der kan opstå et lille ar, de steder hvor der er udtaget hudprøver.
- Formålet med forskningsbiobanken er at samle alle blodprøver og vævsprøver, idet analyserne for biomarkører på inflammation skal foretages samlet, når alle prøverne foreligger.
- Alle analyser på materialet forventes at være afsluttede i januar 2020.
- Hvis der er materiale til overs efter denne dato, vil det blive anonymiseret, hvis det skal opbevares i længere tid.

Procedure ved PET/CT-skanningen:

Du skal faste 6 timer forud for PET/CT- skanningen, men må gerne drikke vand, kaffe/the uden sukker eller mælkeprodukter. Når skanningen begyndes, får du anlagt en nål i en blodåre, som derefter skal bruges til indsprøjtning af en lille mængde radioaktivt mærket sukkerstof. Efter ca. 90-120 minutters ventetid kan skanningen begynde. Til skanningen skal du ligge på et leje på ryggen, imens du bliver kørt igennem hullet på skanneren, som består af to sammenbyggede ringe. Selve PET/CT-skanningen tager ca. 40 minutter, og du skal regne med at være i afdelingen i ca. 2,5-3 timer i alt. Efter skanningen kan du få noget at spise og drikke, inden du tager hjem.

Der er vedlagt kopi af "patientinformationen" for PET/CT-skanning fra PET-Centret, Nuklearmedicinsk og PET, Aarhus Universitetshospital.

Mulig nytte ved forsøget

Hvis du efter tilfældighedsprincippet tildeles aktiv behandling med brodalumab (Kyntheum), kan du forvente, at din psoriasis med stor sandsynlighed afglattes helt eller stort set helt. På sigt kan deltagelsen for dig og andre psoriasis patienter betyde en bedre behandling af både psoriasis i huden men muligvis også af de inflammatoriske processer, som påvirker andre organer. Resultaterne kan også medføre, at patienter i højere grad kan tilbydes individualiseret behandling ud fra kendskab til flere markører for sygdomsaktivitet og følgesygdomme. Studiet forventes at bidrage med viden, der kan afklare, om den forøgede risiko for hjertekarsygdom hos psoriasispatienter vil kunne mindskes ved effektiv behandling af psoriasis. Samtidig vil studiet kunne bidrage med viden omkring den rolle, som inflammation spiller ved åreforkalkningssygdom generelt. Det er desuden muligt, at PET/CT-skanningerne påviser tegn på andre sygdomme, som endnu ikke har givet dig symptomer. F.eks. er det kendt fra flere internationale studier og fra kliniske erfaringer, at der hos nogle patienter kan opdages ondartede knuder i bl.a. tarmsystemet, som endnu ikke har givet symptomer. Med mindre du i situationen tydeligt frabeder dig dette, vil du i så fald straks blive henvist til yderligere undersøgelse og behandling. De forsøgsansvarlige læger og De Videnskabs Etiske Komitéer har vurderet, at nytteværdien ved forsøget opvejer den risiko, som forsøget indebærer.

Bivirkninger ved PET/CT skanning:

I forbindelse med passagen igennem hullet i skanneren oplever personer med klaustrofobi nogle gange ubehag.

Mængden af indsprøjtet radioaktivt sukkerstof og stråler fra PET/CT-skanning er lille og svarer til ca. 3-4 års baggrundsstråling. Strålingen medfører en meget lille øget risiko for at udvikle en uhelbredelig kræftsygdom - teoretisk stiger livstidsrisikoen for at udvikle kræft fra ca. 25 procent til 25.048 procent for personer under 50. For personer over 50 år reduceres denne risiko for at dø af en stråle udløst kræftsygdom, da varigheden til udvikling af kræft er mangeårig, og følsomheden for stråling falder med alderen.

Ulemper ved at deltage i forsøget

Du kan evt. opleve forværring i din psoriasis sygdom, hvis du skal holde en pause fra din behandling inden påbegyndelse af det videnskabelig forsøg, og hvis du bliver randomiseret til at modtage placebo (blindpræparat) i behandlingsperioden. I forbindelse med de første undersøgelser vil forløbet omkring behandlingspause blive aftalt. Du vil altid have mulighed for at komme i kontakt med personalet i forskningsafdelingen og med de forsøgsansvarlige, mens du deltager i forsøget. Det er ikke tilladt at anvende stærke lokalsteroid (binyrebarkhormon) cremer under studiet, da dette vil kunne forstyrre resultatet. Det er dog tilladt at anvende almindelige fugtighedscremer, svage og

middelstærke binyrebarkhormon cremer for at mildne generne fra din psoriasis. Der kan således anvendes en gruppe II steroid creme efter nærmere aftale med de projektansvarlige læger.

I forbindelse med PET/CT-skanningen kan der være gener i form af sult fornemmelse pga. 6-timers faste forud for skanningen. Dertil er der tidsforbrug i forbindelse med selve skanningen og transport til og fra skanningen. Der kan forekomme ekstra ventetid pga. tekniske problemer ved fremstilling af det radioaktivt mærkede sukkerstof.

Brodalumab (Kyntheum) er som anført et godkendt lægemiddel til behandling af moderat til svær psoriasis. De kendte bivirkninger ved brodalumab omfatter ledsmerter, hovedpine, træthed, diarré, smerter i mund/svælg, infektion og svampeinfektioner. Sjældent kan der opstå tendes til et lavt antal hvide blodlegemer (neutropeni).

Registrering og brug af oplysninger i forsøget

I forbindelse med forsøget og kontrol af dette, kan særligt bemyndigede personer, der har tilknytning til forsøget, monitor (GCP-enheden ved Aarhus Universitet), samt Lægemiddelstyrelsen, få direkte adgang til oplysninger i din journal. Disse personer har tavshedspligt og vil behandle dine personlige data strengt fortroligt. Der vil på intet tidspunkt blive udleveret oplysninger, som kan henføres til dig personligt. Oplysningerne vil blive registreret og opbevaret i 5 år efter forsøgets afslutning. Resultaterne af forsøget vil senere indgå i en videnskabelig opgørelse.

Transport

Udgifter til transport i forbindelse med ambulante besøg til lægesamtaler og PET/CT-skanninger refunderes i henhold til gældende retningslinjer. Der gives ikke i øvrigt økonomisk kompensation for deltagelse i forsøget.

Udgang fra forsøget

Lægen, der er ansvarlig for forsøget, kan på et hvilket som helst tidspunkt afslutte forsøget, fx hvis der foreligger en medicinsk begrundelse, en sundhedsrisiko eller et krav fra myndighederne.

Økonomisk forhold:

Projektet er initieret af afdelingslæge Anne Bregnhøj, afdelingslæge Trine Høgsberg og professor, overlæge Lars Iversen, Hud og Kønssygdomme, Aarhus Universitetshospital. De projektansvarlige har ingen økonomiske interesse i studiet.

Driftsomkostninger til gennemførsel af studiet dækkes af en bevilling fra LEO Pharma A/S som administreres via en forskningskonto på Aarhus Universitetshospital. Desuden sponsorerer LEO Pharma A/S den brodalumab (Kyntheum) der anvendes i studiet. LEO Pharma A/S har ikke indflydelse på designet af forsøget, udførelsen af forsøget eller tolkningen af forsøgsresultaterne. Den samlede økonomiske støtte til dækning af ovennævnte udgifter fordelt over hele forsøgsperioden er 212.900 euro (ca. 1.607.000 kr).

Det er frivilligt at deltage i forsøget

Meningen med denne skriftlige information er, at du skal overveje, om du vil deltage i forskningsprojektet. Det er godt at drøfte informationerne med din nærmeste.
Det er din egen frivillige beslutning, om du vil deltage i forsøget. Hvis du beslutter dig for at deltage i forsøget, kræver dansk lov, at du bekræfter dette ved at skrive under på samtykkeerklæringen.

Ved at skrive under giver du tilladelse til, at vi må bruge og videregive resultaterne fra din PET/CT-skanning samt oplysninger i din journal, mellem lægerne og afdelingerne som er involveret i projektet. Dine personlige oplysning vil blive behandlet strengt fortroligt og vil kun blive anvendte til dette projekt. Der vil ikke blive offentliggjort personhenførbare oplysninger.

Føler du, at der bliver lagt pres på dig, råder vi dig til at udskyde afgørelsen. Vælger du at deltage, kan du i øvrigt, når som helst og uden begrundelse, tilbagekalde dit samtykke. Uanset om du siger ja, nej, eller fortryder senere, vil vi give dig den bedst mulige behandling af din sygdom.

Forsøget er godkendt af De Videnskabsetiske Komitéer, Lægemiddelstyrelsen og Datatilsynet. Den Videnskabsetiske Komités hovedopgave er at beskytte forsøgspersoner, der deltager i biomedicinske forsøg og sikre, at man som forsøgsperson frit kan vælge, om man vil deltage.

Hvis du har spørgsmål til projektet, er du velkommen til at kontakte projektets kontaktperson og forsøgsansvarlige.

Vi vil opfordre dig til at læse pjecen "Forsøgspersoners rettigheder i sundhedsvidenskabelige forskningsprojekter" som er vedlagt deltagerinformationen.

Kontaktperson og forsøgsansvarlig

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Informeret samtykke til deltagelse i et sundhedsvidenskabeligt forskningsprojekt.

Forskningsprojektets titel: **Effekten af brodalumab sammenlignet med placebo på inflammation i hovedpulsåren hos patienter med moderat til svær psoriasis**

Erklæring fra forsøgspersonen:

Jeg har fået skriftlig og mundtlig information og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til, at deltage i forskningsprojektet og til, at mit biologiske materiale udtages med henblik på opbevaring i en forskningsbiobank. Jeg har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspersonens navn: _____

Dato: _____ Underskrift: _____

Ønsker du at blive informeret om forskningsprojektets resultat samt eventuelle konsekvenser for dig?:

Ja _____ (sæt x) Nej _____ (sæt x)

Erklæring fra den, der afgiver information:

Jeg erklærer, at forsøgspersonen har modtaget mundtlig og skriftlig information om forsøget.

Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Navnet på den, der afgiver information: Forsøgsansvarlige:

Dato: _____ Underskrift: _____

Projektidentifikation:

EudraCT 2017-003697-14

Deltagerinformation ver. nr.: 2.1, 12.12.2017