CLINICAL STUDY PROTOCOL

A double-blind, multi-center, two-part, randomized, placebo-controlled study of the safety, tolerability, and efficacy of 4 weeks of treatment with AP1189 in early rheumatoid arthritis (RA) patients with active joint disease

Clinical Study Sponsor:	SynAct Pharma ApS	**Clinical Study Phase:**	IIa
Protocol Code:	SynAct-CS002	**Version:**	9.0
Version date:	14. January 2021	**EudraCT No:**	2019-001185-15

1 STUDY ADMINISTRATION

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2 CLINICAL STUDY APPROVAL FORM

The final clinical study protocol, version 9.0, dated 14. January 2021 has been approved by:

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Thomas Jonassen

Date: January 22, 2021

Medical Writer:
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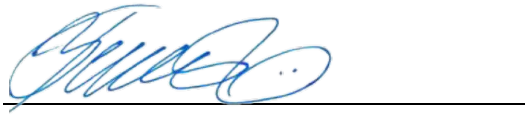

Date: 21JAN2021

Statistician:
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Date: 21JAN2021

3 COMPLIANCE STATEMENT

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practices (GCP) (ICH GCP Guidelines with Integrated Addendum E6(R2)), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

4 INVESTIGATOR AGREEMENT

I have read the attached protocol entitled: *("***A double-blind, multi-center, two-part, randomized, placebo-controlled study of the safety, tolerability, and efficacy of 4 weeks of treatment with AP1189 in early rheumatoid arthritis (RA) patients with active joint disease")**, dated 14 January 2021, and agree to abide by all provisions set forth therein.

I have read the Investigator's Brochure (IB) for the investigational medicinal product (IMP) including the potential risks and adverse drug reactions of the IMP and I agree to report all adverse events which occur during the trial.

I confirm that I am suitably qualified by my education, scientific medical training, and experience to conduct the trial. Documentation of my qualifications and professional affiliations are contained in my signed and dated curriculum vitae.

I agree to comply with the International Conference on Harmonization (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that the study will not be initiated before written approval from the Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) and the Competent Authorities (CA), and that any additional requirements imposed by the IEC/IRB or CA shall be followed, as appropriate.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____

Signature

_____ _____

Printed Name of Principal Investigator Date (DDMMMYYYY)

5 GLOSSARY OF ABBREVIATIONS

%	Percentage
°C	Degree Celsius
αMSH	Alpha-melanocyte stimulating hormone
ACR	American College of Rheumatology
ACTH	Adrenocorticotrophic hormone
ADL	Activity of Daily Living
AE	Adverse Event
ALAT/ALT	Alanine aminotransferase/alanine transaminase
ALP	Alkaline phosphatase
ANOVA	Analysis of variance
Anti-CCP	Anti-Cyclic Citrullinated Peptide
AR	Adverse Reaction
ASAT/AST	Aspartate aminotransferase/aspartate transaminase
ATC	Anatomical Therapeutic Chemical (ATC) Classification System
AUC	Area under the curve
bHLH-LZ	Basic helix-loop-helix leucine zipper
BLQ	Below the Limit of Quantification
BP	Blood Pressure
bpm	Beats per minute
CA	Competent Authorities
Ca^{2+}	Calcium
cAMP	Cyclic adenosine monophosphate
CDAI	Clinical disease activity score
cDNA	Complementary deoxyribonucleic acid
CL/F	Apparent total clearance
CLr	Renal clearance
C_{max}	Maximum plasma concentration
COX	Cyclooxygenase
CRO	Clinical Research Organization
CRP	C-Reactive Protein
CSA	Clinical Study Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of variation
CXCL13	Chemokine ligand 13
DAS28	Disease activity score 28 (28 joints are examined)
DMARD	Disease-modifying anti-rheumatic drugs
DMC	Data Monitoring Committee
DMP	Data Management Plan
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
e.g.	Exempli gratia (for example)

ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
ERK1/2	Extracellular signal-regulated kinase ½
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practices
GGT	Gamma-glutamyl transpeptidase
HAQ-DI	Health Assessment Questionnaire – Disability Index
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonization
i.e.	Id est (that is)
IEC	Independent Ethics Committee
IGA	Investigator Global Assessment
IL	Interleukin
IMP	Investigational medicinal product
IP	Interphalangeal
IRB	Institutional review board
ISF	Investigator Site File
IUPAC	International Union of Pure and Applied Chemistry
kg	Kilogram(s)
LL-R	Ligand Specific Receptor
MAD	Maximum Administered Dose
MC	Melanocortin
MCP	Metacarpophalangeal
MCR	MC receptor
MCTD	Mixed Connective Tissue Disease
MedDRA	Medical dictionary for regulatory activities
mg	Milligram(s)
MITF	Microphthalmia-associated transcription factor
ml	Millilitre
mm	Millimetre(s)
mmHg	Millimetre mercury
mRNA	Messenger ribonucleic acid
MTD	Maximum Tolerated Dose
MTX	Methotrexate
N	Number of observations

ng	Nanogram
NFκB	Nuclear Factor Kappa-B
NSAID	Nonsteroidal anti-inflammatory drugs
PGA	Patient Global Assessment
PIP	Proximal interphalangeal joint
PK	Pharmacokinetic
PRO	Patient-Reported Outcome questionnaire
QFG-IT	QuantiFERON-in-Tube test
QT	QT interval
QTcF	Corrected QT interval by Fredericia
RA	Rheumatoid arthritis
RBC	Red blood cell
RoI	Resolution of Inflammation
RF	Rheumatoid factor
SAD	Single Ascending Dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SC	Steering Committee
SD	Standard Deviation
SDV	Source data verification
SJC	Swollen joint count
SLE	Systemic Lupus Erythematosus
SPC	Summary of Product Characteristics
SPM	Specialized Pro-Resolving Mediators
Sqrt	Square
SSI	Statens Serum Institut
SUSAR	Suspected unexpected serious adverse reaction
T½	Apparent terminal elimination half-life
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TJC	Tender joint count
TMF	Trial Master file
TNFα	Tumor necrosis factor alpha
T_{max}	Time at which the C_{max} is observed
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid stimulation hormone
VAS	Visual Analog Scale
Vd/F	Apparent volume of distribution
WBC	White blood cell
WD	Withdrawn

µSV	Microsivert

6 TABLE OF CONTENTS

7 PROTOCOL SYNOPSIS

Protocol title	A double-blind, multi-center, two-part, randomized, placebo-controlled study of the safety, tolerability, and efficacy of 4 weeks of treatment with AP1189 in early rheumatoid arthritis (RA) patients with active joint disease
Protocol no	SynAct-CS002
Clinical phase	IIa
Estimated study duration	Study duration: 18 months Study participation for each subject is estimated to 10 weeks
Study design	A multicenter, two-part, randomized, double-blind, placebo-controlled, 4-week study with repeated doses of AP1189. The study population will consist of newly diagnosed subjects with severe active RA (CDAI (Clinical disease activity score) > 22) who are to start up-titration with methotrexate (MTX). Part 1: The subjects will be randomized into: • Group A: AP1189 dose 50 mg (min. 8 subjects) or • Group B: placebo (min. 4 subjects) Steering Committee (SC) meeting • Group C: AP1189 dose 100 mg (min. 8 subjects) or • Group D: placebo (min. 4 subjects) INTERIM ANALYSIS Part 2: All subjects will be randomized into either design 1, 2 or 3 based on data from the interim analysis. • Design 1: AP1189 dose 50 mg (44 subjects) or placebo (22subjects) plus MTX (10-25 mg) weekly • Design 2: AP1189 dose 100 mg (44 subjects) or placebo (22 subjects) plus MTX (10-25 mg) weekly • Design 3: Continue with the same doses as in Part 1, in a 1:1:1 ratio (AP1189 50 mg (22 subjects), AP1189 100 mg (22 subjects) or

	placebo (22 subjects)) plus MTX (10-25 mg) weekly
Study sites	The study is to be conducted at sites in Europe and Moldova
Treatment duration	Multiple dose administration consisting of once-daily dosing from Day 1 to Day 28, preceded by a screening period of up to 2 weeks before the first dosing. A 4 weeks safety follow-up period will follow the last dose administration
Study population	Subjects with severe active RA, defined as CDAI > 22, who are about to begin up-titration with MTX
Study objectives	Primary safety objective: • To compare the safety of AP1189 against placebo by evaluating adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities Primary efficacy objective: • Effect of AP1189 vs. placebo in subjects with severe active RA (CDAI > 22), undergoing up-titration with MTX, by showing a change in CDAI from severe (CDAI > 22) to moderate (CDAI ≤ 22) after 4 weeks treatment compared to baseline Secondary efficacy objectives: To compare the effects of AP1189 against placebo by assessing: • Proportion of subjects achieving a reduction of more than 10 (ten) swollen and/or tender joints at week 4 compared to baseline • Proportion of subjects achieving a change in CDAI score at week 4 compared to baseline o Proportion of subjects with a 5-point decrease o Proportion of subjects with a 10-point decrease o Proportion of subjects with a 15-point decrease • Proportion of subjects achieving a change in value to ≤ 3.2 as measured by

	DAS28 (disease activity score 28) at week 4 compared to baseline • Change in subject-reported quality of life (using Health Assessment Questionnaire – Disability Index (HAQ-DI)) at week 4 compared to baseline • Change in subject-reported fatigue (using Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue) at week 4 compared to baseline • Proportion of subjects achieving ACR (American College of Rheumatology) response assessed by ACR 20, ACR 50, and ACR70 Tertiary objectives: Effect of AP1189 compared to placebo at week 4 compared to baseline on inflammatory and collagen destructive biomarkers. The biomarkers include: • CXCL13 (chemokine ligand 13) • IL-1β (interleukin 1 beta) • IL-6 (interleukin 6) • IL-10 (interleukin 10) • TNF-α (tumor necrosis factor alpha) Arthroscopy Sub-Study (only Part 2 at selected sites): • Effect of AP1189 compared to placebo on joint structures and inflammation as assessed by synovial biopsy at baseline and after 4 weeks treatment
Investigation product	AP1189 powder in bottle
Reference product	Placebo powder in bottle
Main criteria for inclusion	1. Written informed consent has been obtained prior to initiating any study specific procedures 2. Male and female subjects, 18 to 85 years of age 3. Confirmed diagnosis of RA according to the 2010 ACR/EULAR RA classification criteria 4. Arthritis with joint swelling and tenderness of a minimum of three joints out of 68 joints tested 5. Candidate for MTX treatment 6. Is about to begin treatment with MTX

	7. Tested positive for anti-Cyclic Citrullinated Peptide (anti-CCP) or rheumatoid factor (RF) 8. Severe active RA (CDAI > 22) at screening and baseline 9. Negative QuantiFERON-in-Tube test (QFG-IT) (Mantoux test can be used if QFG-IT is not possible) 10. Subjects should be able to complete (read and write) the Patient-Reported Outcome questionnaires (PRO questionnaires) 11. Females of child-bearing potential may only participate if using reliable means of contraception (for detailed information see section 17.8) or are post-menopausal (menstrual periods stopped at least 12 months ahead of the enrolment in the trial) Surgically sterilized women at least 6 months prior to screening 12. Females of childbearing potential must have a negative pregnancy test at screening and baseline
Exclusion criteria	1. Participation in any other study involving investigational drug(s) within 4 weeks prior to study entry 2. Major surgery (including joint operation) within 8 weeks prior to screening or planned surgery within 1 month following randomization 3. Rheumatic autoimmune disease other than RA, including systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), scleroderma, polymyositis, or significant systemic involvement secondary to RA (e.g., vasculitis, pulmonary fibrosis or Felty's syndrome). Sjögren's syndrome with RA is allowable 4. Functional class IV as defined by the ACR Criteria for Classification of Functional Status in RA or wheelchair/bedbound 5. Prior history of or current inflammatory joint disease other than RA (e.g., gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease) 6. Subjects with fibromyalgia 7. Initiation or change in dose for NSAIDs (including low-dose aspirin and COX-2

	inhibitors) within 2 weeks prior to dosing with IMP 8. Corticosteroids are prohibited within 2 weeks prior to screening (and during the entire treatment period and until the final visit (Visit 7) 9. Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus), or gastrointestinal disease 10. Have prior renal transplant, current renal dialysis, or severe renal insufficiency (determined by a derived glomerular filtration rate (GFR) using Cockcroft Gault formula of ≤30 ml/min/1,73m² calculated by the local lab) 11. Uncontrolled disease states, such as asthma, psoriasis, or inflammatory bowel disease where flares are commonly treated with oral or parenteral corticosteroids 12. Evidence of active malignant disease (except basal cell carcinoma of the skin that has been excised and cured) 13. Pregnant women or nursing (breastfeeding) mothers 14. History of alcohol, drug, or chemical abuse within the 6 months prior to screening 15. Neuropathies or other painful conditions that might interfere with pain evaluation 16. Body weight of >150 kg **EXCLUSION CRITERIA 17-20 ONLY APPLY FOR SUBJECTS IN NORWAY:** 17. Evidence of moderate and/or severe organ dysfunction 18. Abnormal chest x-ray (as per the discretion of the investigator) 19. Evidence of positive hepatitis serology 20. Evidence of peptic ulcer disease
Sample size considerations	The sample size is calculated to provide an acceptable precision of a 95% confidence interval for the primary endpoint, the mean change in CDAI from baseline.

8 INTRODUCTION AND RATIONALE

8.1 Introduction

Inflammatory processes play a pivotal role in health and disease, not only in classical inflammatory diseases as arthritis and inflammatory bowel disease (IBD) but also in major lifestyle associated diseases as diabetes and atherosclerosis.

Inflammatory processes consist of an acute phase induced by an injury where inflammation is initiated and dominated by proinflammatory reactions. The inflammation will subsequently either be resolved, and the system will go back to normal physiological status or alternatively develop further and enter into a more chronic phase. The chronic phase is dominated by irreversible and deleterious effects on tissues and organs and thus impact the overall body hemostasis.

Until recently pro-resolving processes, i.e., processes that facilitate the restoring of a normal physiological steady state, have been considered passive. Most treatment concepts have been focusing on pro-inflammatory pathways and leucocyte recruitment, and thereby on the possibility to reduce the severity of the acute phase of the inflammation. The only major treatment concept available to reduce the severity in established inflammatory processes is the use of corticosteroids, which, unfortunately, do have several unwanted adverse effects when administrated in a daily dose regimen.

8.2 Resolution of Inflammation

Today pro-resolving processes are considered active processes and the scientific field of resolution of inflammation (RoI) is one of the most promising fields of today´s inflammatory research. A key point within RoI is the identification of specialized pro-resolving mediators (SPM) signaling through specific receptors present in immune competent cells, including the white blood cells.

A key feature of SPM is that they, besides the classic anti-inflammatory effects such as inhibition of pro-inflammatory cytokine secretion and inhibition of neutrophils recruitment and infiltration, have specific effects on processes that stimulate RoI. Therefore, the most fundamental effect of SPM that discriminate them from classic anti-inflammatory mediators is SPM´s ability to stimulate non-phlogistic activation of macrophages, which means that SPM is able to stimulate macrophages to clear the inflammatory process from apoptotic neutrophils and microbial particles by efferocytosis. The result is that SPM can facilitate RoI and thereby speed up the processes that bring the system back to a normal physiological steady state and reduce the risk of developing chronic and thus treatment-resistant conditions[1].

An example of an endogen system playing a significant role in RoI is the melanocortin (MC) system, where the peptide α-melanocyte stimulating hormone (αMSH) is secreted from white cells and other immune competent cells and binds to MC receptors (MCRs) and thereby facilitates RoI. Consequently, the effects are mediated in a paracrine and autocrine fashion (i.e., signaling local within a tissue/organ by stimulation of adjacent cells or even the cells that secrete the SPM).

The understanding of this system including the understanding of how to target the systems by use of an agonist to the MCRs makes the MC system a very attractive target for pharmaceutical development.

8.3 The Melanocortin System

The immune modulation effects of the MCs have been known for more than two decades. With the identification of specific receptors and the development of new analogues with improved properties over those of the natural agonist αMSH. Some development projects have been set up that aimed to use the potential of these peptides as anti-inflammatory and/or organ protective agents. Natural peptides, especially adrenocorticotrophic hormone (ACTH) and αMSH, as well as synthetic analogues as the AP1189 peptide, are anti-inflammatory and have organ protective effects in several in vivo models[2]. In addition, it has been shown that that MCs induce pro-resolving effects as phagocytosis and efferocytosis[3], which gives new aspect for MC-based therapy.

8.4 Melanocortin Receptors

MC binds to MCRs. Five subtypes of MCRs have been described, all are G-coupled receptors, where the ability to stimulate cyclic adenosine monophosphate (cAMP) in the different subtypes of MCRs have been used to characterize the agonist's potency and specificity. They are described in the next sections (from Catania et al.[4]). A central role in the anti-inflammatory effects of MCR stimulation has been explained by the ability to inhibit activation of the transcriptions factor nuclear factor-kappa B (NFκB) and thereby the ability to inhibit synthesis and secretion of pro-inflammatory mediators.

In addition to this classical cAMP-mediated pathway, MCR stimulation also has the potential to stimulate other pathways associated with extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation, and intracellular calcium (Ca^{2+}) mobilization[5]. In a broader aspect, this raises the possibility that MCRs shows functional selectivity, alternatively called biased agonism, i.e., that the MCRs exists in different active conformations, each one creating a distinct signal yielding to multiple functional outcomes. If this is the case, then it could potentially be possible to identify compounds that would be able to induce the classical cAMP pathway and not ERK1/2 phosphorylation, and intracellular Ca^{2+} mobilization and other compounds stimulating ERK1/2 phosphorylation, and intracellular Ca^{2+} mobilization, but not cAMP generation.

8.4.1 MC1 Receptor (MC1R)

MC1R was the first member of the MCR gene family to be cloned. The cloned complementary deoxyribonucleic acid (cDNA) encoded a 317-amino acid protein with the transmembrane topography characteristic of receptors that couple to heterotrimeric G proteins. αMSH/MC1R interactions contribute to regulation of skin physiology and melanogenesis[6]. Binding of αMSH to its MC1R in melanocytes starts a signal cascade that activates adenylyl cyclase, increases intracellular cAMP, and induces activity of tyrosinase, the rate-limiting enzyme in the eumelanin synthetic pathway[7, 8]. MC1R messenger ribonucleic acid (mRNA) in the skin is up-regulated by its own melanocortin ligands and by endothelin-1[9]. Furthermore, MC1R expression appears to be regulated by the microphthalmia-associated transcription factor (MITF). This transcription factor belongs to the family of bHLH-LZ (basic helix-loop-helix leucine zipper) type transcription factors and promotes transcription of genes for melanogenesis-related enzymes such as tyrosinase. It is clear that MC1R functions extend well beyond regulation of melanogenesis. MC1R expression occurs in macrophage/monocytic cells, lymphocytes with antigen-presenting and cytotoxic functions, neutrophils, endothelial cells, astrocytes, and fibroblasts. Peripheral blood-derived dendritic cells were likewise found to express. Transactivation of MC1R in inflammatory cells causes marked reduction of activation and translocation to the nucleus of the transcription factor NFκB[10]. Consequently, there are marked anti-inflammatory effects exerted through inhibition of NFκB -mediated

transcription. Although receptor density in inflammatory cells is less than that in melanocytes, it appears that receptor affinity is much greater.

8.4.2 MC2 Receptor (MC2R)

MC2R, also known as ACTH receptor, is selectively activated by adrenocorticotropic hormone. The ACTH receptor/MC2R gene was originally isolated by homology screening of human cDNA and genomic DNA libraries. The ACTH receptor gene encodes a 297-amino acid G protein-coupled receptor and shows the characteristic seven transmembrane spanning domains that form the ligand binding site. The physiological influences of ACTH on production and release of steroids by the adrenal cortex, their circadian variation, and stress-related fluctuations are mediated by MC2R[11, 12]. Binding of ACTH to its receptor stimulates adenylyl cyclase and induces increases in cell cAMP; this leads to activation of protein kinase A, which promotes expression of steroidogenic enzymes. In situ hybridization studies revealed dense expression of MC2R in the zona glomerulosa and zona fasciculata of the adrenal cortex13, the sites of mineralocorticoid and glucocorticoid production. The zona reticularis showed less mRNA labeling. MC2R expression in adrenal cells is upregulated by its ligand ACTH. In addition to the adrenal glands, the MC2R mRNA has been found in murine adipocytes, where it is believed to mediate stress-induced lipolysis in response to ACTH[14]. However, ACTH does not appear to regulate adipocyte function in humans and other primates, as human adipocytes lack expression of MC2R[15].

8.4.3 MC3 Receptor (MC3R)

MC3R gene encodes a G protein-linked receptor, coupled to both cAMP - and inositol phospholipid - Ca^{2+} - mediated signaling systems. The MC3R is the only MCR activated by γMSH with potency similar to that of other. MC3R expression occurs in brain, placenta, and gut but not in melanoma cells or in the adrenal gland[16]. MC3R expression also occurs in the heart, in human monocytes, and in mouse peritoneal macrophages. A map of MC3R expression in the brain obtained by *in situ* hybridization showed abundant presence in the hypothalamus and limbic system, but signals for this receptor were also present in the septum, thalamus, hippocampus, and midbrain[17]. MC3R appears to participate in modulation of autonomic functions, feeding, and inflammation[18]. Hypotension and bradycardia elicited by the release of αMSH from the arcuate neurons appear to be mediated by MC3R and MC4R located in the medullary dorsal-vagal complex[19]. Participation of MC3R in energy homeostasis was disclosed in MC3R-deficient mice, which showed increased fat mass, reduced lean mass, and higher ratio of weight gain to food intake[20]. Recent data suggest that MC3R activation mediates protective influences of MC's in myocardial ischemia/ reperfusion-induced arrhythmias in rats[21]. Furthermore, activation of MC3R has clear anti-inflammatory influences[22].

8.4.4 MC4 Receptor (MC4R)

MC4R was the second neural MCR to be cloned. Its affinity for the melanocortins has certain similarities with that of MC1R. The order of potency for activation of MC4R is αMSH = ACTH > βMSH >> γMSH. MC4R is a 332-amino acid protein encoded by a single exon of 999 nucleotides. The rat homologous gene is 93% identical to the human gene[23], which suggests that the gene is highly conserved in mammals. By the use Northern blot analysis and *in situ* hybridization techniques, MC4R was found primarily in the brain. The distribution of this receptor in the central nervous system is much broader than that of MC3R and includes the cortex, the thalamus, the hypothalamus, the brainstem, and the spinal cord[24]. Conversely, the MC4R was not detected in peripheral cells in an extensive study including 20 different tissues. Distribution of MC4R is consistent with its involvement in autonomic and neuroendocrine functions. Evidence that this receptor subtype regulates food intake and energy expenditure is based on gene-targeting in mice, which results in maturity-onset obesity, with

hyperphagia, hyperinsulinemia, and hyperglycinemia. Homozygous MC4R-deficient mice do not respond to the anorectic effects of αMSH. It appears, therefore, that αMSH inhibits food intake through activation of MC4R[25]. Mice with MC4R deficiency have enhanced caloric efficiency, like that observed in the agouti obesity syndrome and in the MC3R-null mice. Mice lacking both MC3R and MC4R are significantly heavier than those deficient in MC4R only, suggesting that the two receptors serve nonredundant functions in the regulation of energy homeostasis. Research also indicates that MC4R modulates erectile function and sexual behavior, possibly through neuronal circuitry in spinal cord erectile centers and somatosensory afferent nerve terminals of the penis[26].

8.4.5 MC5 Receptor (MC5R)

MC5R is similar to the MC1R and MC4R in its capacity to recognize αMSH and ACTH but not γ-MSH (αMSH ≥ ACTH >> γ-MSH). MC5R contributes to regulation of exocrine gland function and to certain immune responses. The MC5R was the last of the MCR gene family to be cloned. The human gene encodes for a protein of 325 amino acids. MC5R is ubiquitously expressed in peripheral tissues. It occurs in the adrenal glands, fat cells, kidney, liver, lung, lymph nodes, bone marrow, thymus, mammary glands, testis, ovary, pituitary testis, uterus, esophagus, stomach, duodenum, skin, lung, skeletal muscle, and exocrine glands. Presence of MC5R in B- and T-lymphocytes suggests a function in immune regulation. Indeed, data suggest that αMSH participates in B-lymphocyte function via the activation of the Jak/STAT pathway, the intracellular phosphorylation pathway used by cytokines and growth factors, through specific binding to the MC5R. Furthermore, αMSH can induce $CD25^+$ $CD4^+$ regulatory T cells through the MC5R expressed on primed T cells[27]. Targeted disruption of the MC5R gene produced mice with a severe defect in water repulsion and thermoregulation caused by decreased production of sebaceous lipids[28]. High expression of MC5R occurs in multiple exocrine tissues, and the receptor is required for production of porphyrins by the Harderian gland and for protein and tear secretion by the lacrimal gland. These data suggest a coordinated system for regulation of exocrine gland function by melanocortin peptides; also, that the MC5R is the mediator of the sebotrophic activity of αMSH described in early studies[29].

8.4.6 Anti-inflammatory Effects of Melanocortins

The anti-inflammatory effects of MCs are exerted through inhibition of inflammatory mediators and by inhibition of inflammatory cell migration. MCs exert these effects in a variety of cells including monocytes, macrophages, subtypes of T-cells, endothelial cells, and epithelial cells. It is thought that the main pathway for the anti-inflammatory effect is through MC1R and MC3R stimulation.

Most cell types responsive to the anti-inflammatory effect of MCs express the MC1R, i.e., monocytes, macrophages, neutrophils, mast cells, fibroblasts, dendritic cells, astrocytes, and microglia. Both human and murine macrophages among other cell types express the MC3R, and an increasing number of reports have identified MC3R mediated anti-inflammatory effects *in vitro* and *in vivo* in models of both acute and more sustained/chronic inflammation. Of specific interest are recent findings that anti-inflammatory effects on αMSH and other non-specific MCR agonists are absent in disease models in MC3R -/- mice, suggesting a profound role of MC3R in the anti-inflammatory effects of MCs. Furthermore, selective MC1R agonists have been shown to lack organ protective effects in models of ischemia-reperfusion including models of myocardial infarction. On the other hand, it has recently been shown that long term treatment of the selective MC1R agonists MS05 has beneficial effects in a model of nephrotic syndrome[30]. Consequently, anti-inflammatory intervention reaching the MC system should most likely be targeting both the MC1R and MC3R.

9 NON-CLINICAL STUDIES

9.1 Summary of pre-clinical Studies

The non-clinical development program on AP1189, including toxicology and safety pharmacology studies, was conducted in accordance with the International Conference on Harmonization (ICH) Guideline entitled 'Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals'[53].

All relevant information on the methodologies and the study results are detailed in the Investigator Brochure.

10 CLINICAL STUDIES

10.1 Phase I Study Results

In the phase I study, the first dose of AP1189 in healthy volunteers was administered in single ascending dosing using a suspension for oral administration (SynActCS001 Part I), in a bioequivalence study using oral suspension as well as tablets (SynActCS001 Part II) and in 14 days repeated dosing. Fourteen days repeated dosing was initiated using a tablet formulation (SynActCS001 Part III) and was completed (SynActCS001 Part IV) using the same suspension used in Part I.

A total of 111 subjects were randomized: 104 young healthy male volunteers and eight (8) post-menopausal women. In Part I, 56 subjects received a single oral dose on one occasion (42 received AP1189 and 14 subjects received placebo). In Part II, eight (8) subjects received one single AP1189 oral dose in three occasions separated by one-week wash-out. In Part III, eleven (11) subjects received a single oral dose daily for 14 days (8 subjects received AP1189 and three (3) placebo) and finally in Part IV; thirty-six (36) subjects were treated with AP1189/ placebo once daily for 14 days (27 subjects received AP1189, and nine (9) received placebo).

10.1.1 Summary of Results from Phase I; Part I, II and III

As planned per protocol, the study Part I and II were completed. Study Part I was a randomized, double-blind, placebo-controlled, single ascending dose study with AP1189 or placebo administered as an oral suspension. Seven male groups with healthy volunteers (48 males), and 1 female group with 8 healthy female post-menopausal volunteers (defined by at least a two-year amenorrhea period and an FSH level >30 I.U/L.) received a single ascending dose with AP1189/ placebo administered as an oral suspension of IMP dissolved in SyrSpend ALKA in fasting conditions. The two first male groups were composed of 3 subjects receiving active and one subject placebo; the other groups consisted of 6 subjects receiving active IMP and two subjects receiving placebo. Forty-eight (48) healthy male volunteers aged 19 to 39 years and eight (8) healthy postmenopausal female volunteers, aged 47 to 60 years were included.

The male subjects were treated with oral suspensions with doses in the range of 15-800 mg active IMP (15 mg, 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, or 800 mg) or placebo. The females were treated with 400 mg active IMP or placebo suspensions.

Pharmacokinetic (PK) results showed that in male subjects on the dose range 50 - 800 mg, AP1189 was rapidly absorbed with a median t_{max} (time at which the C_{max} is observed) between 1 and 4 hours. The inter-individual variability was low to moderate for C_{max} (maximum plasma concentration) and AUCs (area under the curve) (< 36%). Mean t1/2 was near to 20 h (CV% < 20%).

Mean Vd/F was between 556 and 784 L with a CV% below 35% and mean CL/F was between 20.26 and 31.26 L/h with a CV% below 50%.

In female subjects, after administration of 400 mg of AP1189, C_{max} and AUCs were slightly increased compared to male subjects. The apparent clearance was lower in the female population (17.26 L/h) and the apparent volume of distribution was similar. However, statistically, no conclusion could be made on the gender effect.

Twenty (20) subjects reported a total of 38 Treatment-Emergent Adverse Events (TEAEs). All TEAEs were of mild (27) or moderate (11) severity. No severe AEs nor serious AEs were reported during the study. Twenty-two (22) of the 38 TEAEs were considered related to the study treatment: 21 of these events were after administration of 200 to 800 mg AP1189, and one event was after the administration of placebo.

The most frequent related TEAEs were gastrointestinal disorders (19 events reported by fourteen (14) subjects): nausea (7 events), abdominal pain (5 events), vomiting (3 events), diarrhea (2 events), abdominal distension (1 event) and dyspepsia (1 event). The frequency of these related TEAEs increased with the dose. Nevertheless, the amount of vehicle in the suspension increased with the dose leading to a consistency and taste increase of the study medicine. This change of consistency and taste of the suspension could be involved in this effect. Amongst the TEAEs considered as not related, headache was reported by seven (7) subjects. Other TEAEs were sporadic.

Some mean changes and individual abnormalities were observed on laboratory parameters, vital signs, and ECG parameters. Most of these changes and abnormalities were limited and considered as not clinically significant.

A total of four (4) male subjects treated with active IMP had isolated increases in aminotransferases (no concomitant changes in alkalic phosphatases or bilirubin were reported). The increases, which reached up to 1.6 above the normal upper value of ALT were observed in one (1) subject treated with 400 mg, two (2) subjects treated with 600 mg and one (1) subject treated with 800 mg. No increases in aminotransferases above the normal upper range were seen in placebo-treated subjects.

No treatment-related changes in vital signs were observed.

No AP1189 associated increases in QTcF (the corrected QT interval by Fredericia) nor changes in any other cardiac parameters were identified during continuous 24-hours 1000 HZ Holter ECG recording evaluation.

Based on the safety evaluation, it can be concluded that the maximum tolerated dose (MTD) was not reached. At the maximum administrated dose (MAD) the exposure obtained was more than 10x above what is expected to be the exposure level for obtaining therapeutic efficacy. Therefore, it was decided not to continue to dose escalation above 800 mg.

Study Part II was a comparative bioavailability study of an AP1189 tablet vs. the oral suspension with additional assessment of food effect following administration of the tablet, according to a three-way cross-over design. A 200 mg AP1189 dose administered once as an oral suspension, and on two separate occasions as two 100 mg AP1189 tablets; once during fasting conditions and once after a high-fat breakfast were tested. The results following dosing with the suspension confirmed the findings from study part 1. Data from the administration of the tablet showed lower exposure with higher variability compared to data from the suspension.

Based on results from the Study Part I and II, it was decided in Part III to investigate, daily doses of AP1189 tablets of 100 mg (Group 1), 200 mg (Group 2) and 400 mg (Group 3) respectively. Part III was designed as a

randomized, double-blind, placebo-controlled, multiple ascending dose study with AP1189 administered as tablets.

The pharmacokinetic (PK) results obtained in Group 1 of the Study Part III, after a 14-day repeated dose, showed a high and unpredicted degree of bioavailability both within and between subjects. Exposure judged on Cmax was seen in the span from below the limit of quantification (BLQ) up to levels expected to be more than three times the exposure expected to induce therapeutic effects. Consequently, it was decided by the sponsor to interrupt the study with the tablet formulation.

Due to the good safety and PK results obtained with the oral suspension in the Study Part I, the sponsor decided to amend the study by adding a Part IV to the study that was identical to Study Part III but conducted with the oral suspension in fasting conditions, allowing to evaluate properly study objectives.

10.1.2 Summary of Result from Part IV

Study Part IV was a randomized, double-blind, placebo-controlled, repeat dose study with AP1189 or placebo administered as an oral suspension given once daily for 14 days. Three cohorts of 12 subjects (9 on active; 3 on placebo) each were dosed with the same formulation as used in part 1 of the study. The dose levels tested were 50mg, 100mg or 200 mg with matching placebo.

10.1.3 PK, Part IV Cohort 1

The dose was 50 mg once daily.

The detailed PK report supports this data. C_{max} was observed between 1- and 2.5-hours post-dose regardless of the day of dosing. Steady state was achieved on Day 7 with C_{max} around 180 ng/mL, which is expected to be the exposure level needed to induce efficacy.

10.1.4 PK, Part IV Cohort 2

The dose was 100 mg once daily.

The PK analysis showed a steep increase in the plasma concentration, as expected, and reached C_{max} around 400 ng/ml at steady state, i.e., a peak increase by approximately 2-fold, when compared to findings in cohort 1.

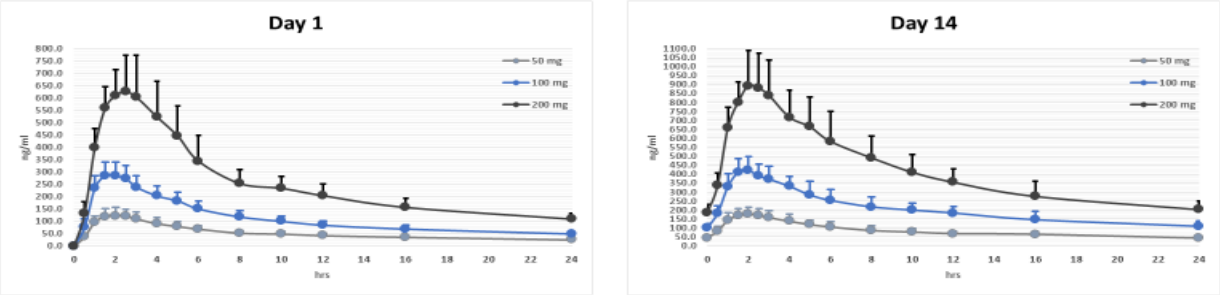
10.1.5 PK, Part IV Cohort 3

The dose was 200 mg once daily.

As for the two other cohorts, C_{max} was reached within 1-2 hours post dosing. C_{max} levels reached up to 900 ng/ml (group average) with the highest measured level of 1.300 ng/ml. As the expected peak exposure needed to induce therapeutic efficacy is expected to be around 170-180 ng/ml, the exposure at the 200 mg dose levels, based on C_{max} is up 5x and for the individual with the highest exposure more than 7x expected therapeutic range.

Based on the PK profile obtained in part 4 of the study, the effective dose using the AP1189 in SyrSpend ALKA would be expected to be around 50 mg.

AP1189-CS001- Part 4 PK MAD suspension- Prelim data.



Mean±SD; n=9 per group

Mean±SD; n=9 per group

10.1.6 Safety Conclusion from Part 4

Fourteen (14) subjects reported a total of 35 Treatment-Emergent Adverse Events (TEAEs). All TEAEs were of mild (27) or moderate (8) severity. No severe AEs nor serious AEs were reported during the study. Four (4) of the 35 TEAEs were considered possibly related to the study treatment. These 4 events were all related to gastrointestinal disorders were seen after administration of the investigational drug (two (2) in the same subject at the 50 mg dose level (one episode of diarrhea and one episode of abdominal cramp, two (2) in the same subject at the 200 mg dose level (one episode of nausea and one episode of vomiting). Amongst the TEAEs considered as not related, headache was reported by nine (9) subjects, seven (7) treated with the investigational drug and two (2) treated with placebo. Other TEAEs were sporadic.

Some mean changes and individual abnormalities were observed on laboratory parameters, vital signs, and ECG parameters. Most of these changes and abnormalities were limited and considered as not clinically significant. The QTcF evaluation from continuous 1000 Hz Holter ECG recording performed on day 14 and compared t Day-1 (baseline) is still ongoing based on exposure/response statistical analysis as recommended by Agencies in FIH. No individual QTcF clinically significant values were observed at any time of this study part in repeated standard 12 lead safety ECG.

A total of five (5) subjects all included in Cohort 3 (200 mg), three (3) treated with active and two (2) treated with placebo had isolated increases in aminotransferases (no concomitant changes in alkalic phosphatases or bilirubin were reported). The increases were most pronounced in the subjects treated with active where the increase reached up to 3.6x and 2.9x above the normal upper value (ALT). All values returned to normal following completion of the study.

Based on the safety evaluation, it can be concluded that MTD was not reached. At the maximum administrated dose (MAD) the exposure obtained 5x above what is expected to be the exposure level for obtaining therapeutic efficacy. Therefore, it was decided not to continue to dose escalation above 200 mg daily.

Consequently, AP1189 present a good safety profile allowing its administration to patients at 50 mg or 100 mg doses for four weeks.

Additional information regarding AP1189, including its physicochemical properties and the results of in vitro and in vivo non-clinical studies of its pharmacology, pharmacokinetics, and toxicology, is presented in the IB.

11 INDICATION

11.1 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a progressive, systemic autoimmune disease characterized by inflammation of the synovium leading to irreversible destruction and disability of the joints and adverse psychological effects. RA patients have fatigue, anemia, and osteopenia. Rheumatoid arthritis primarily affects women with twice the rate compared with men and the prevalence of RA is approximately 0.5-1 % of the population of developed regions with a 4-fold higher frequency in women than in men[31]. There is considerable evidence for both genetic and environmental contributions and a peak incidence of onset between 40 and 60 years of age[32].

Conventional RA therapy consists of treatment with NSAIDs, corticosteroids, and disease-modifying anti-rheumatic drugs (DMARD). MTX represents one of the most widely used DMARD for RA, yet less than half of the patients with RA show substantial and sustained clinical improvement in disease signs and symptoms[33].

Interleukin-6 (IL-6) is a proinflammatory, multifunctional cytokine produced by a variety of cell types. IL-6 is involved in such diverse processes as T-cell activation, B-cell differentiation, induction of acute phase proteins, stimulation of hematopoietic precursor cell growth and differentiation, promotion of osteoclast differentiation from precursor cells, proliferation of hepatic dermal and neural cells, bone metabolism, and lipid metabolism[34, 35, 36, 37, 38]. IL-6 has been implicated in the pathogenesis of a variety of diseases including autoimmune diseases, osteoporosis, neoplasia, and aging[34, 35]. IL-6 exerts its effects through a ligand-specific receptor (IL-6R) present both in soluble and membrane-expressed forms.

Elevated IL-6 levels have been reported in the serum and synovial fluid of RA patients, indicative of production of IL-6 by the synovium[39, 40]. IL-6 levels correlate with disease activity in RA[39], and clinical efficacy is accompanied by a reduction in serum IL-6 levels[41].

Despite the considerable list of approved treatments for RA, there are significant numbers of patients who do not achieve remission or indeed an adequate reduction in disease activity.

11.2 AP1189, an anti-inflammatory lead Compound

AP1189 is an oral available immune modulating compound with both anti-inflammatory and pro-resolving effects targeting the MC-system. Receptor pharmacology has defined AP1189 as a biased agonist on the MC1R and MC3R mediating its pharmacological effects through activation of the ERK1/2 pathway and by Ca^{2+} mobilization. Of specific interest is that AP1189 do not stimulate the cAMP pathway in relevant test systems and therefore through non-cAMP mediated pathways have the ability to induce anti-inflammatory and pro-resolving effects without inducing the unwanted side effect of pigmentation through cAMP stimulation in melanocytes.

Non-clinical data, generated on AP1189, indicates that this drug candidate can be further developed into a pharmaceutical product with unique properties in inflammatory diseases. Currently, there are no anti-inflammatory drugs on the market with a mechanism of action like that of AP1189.

AP1189 is, in contrast to peptide analogs of αMSH, oral available with a PK profile that gives the possibility to apply a once-daily dosing regimen in clinical development.

11.3 Rationale for the Study

The melanocortin as a target for immune modulation therapy is well described. The potential for classical agonist inducing anti-inflammatory and/or organ protective effects has been described in numerous publications over the last two decades and development programs aiming to bring compounds to market has been ongoing for the last decade. Among these projects is the AP124/ABT-719 program with a peptide agonist to the melanocortin peptides that have been dosed to more than 300 cardiac surgery patients at risk for developing post-operative loss of kidney function.

In the US, the Acthar gel has now reached an annual sale of above 1.4 billion $. The active ingredient in the compound is ACTH. ACTH mode of action is two-fold, it stimulates glucocorticoid release from the adrenal glands, and it has direct anti-inflammatory effects on inflamed tissue/organs. The effects on the adrenal glands are mediated through the ACTH specific MC2R, whereas the direct anti-inflammatory effects are mediated through stimulation of MC1R and MC3R. Importantly there is increasing evidence that the MC2R mediated effects merely are unwanted side-effects (as skin pigmentation) of the ACTH derived therapy, which in any case limits the use of Acthar gel to the difficult to treat cases where standard treatment has shown to be insufficient. Acthar gel is used for nephrotic syndrome, multiple sclerosis, and rheumatoid diseases, where the effects of the compound are significant, even though the compound is limited to treat difficult cases. Consequently, compounds directly targeting the MC1R and MC3R without unwanted effects mediated through MC2R stimulation would be an advantageous approach.

Classical MCR agonists, as the endogen αMSH or the AP214/ABT-719 mentioned above, activate the MCRs through classical Gs-mediated pathways thereby inducing intracellular cAMP accumulation. Recent publications have shown that the MCRs can be activated not only to induce cAMP but also to induce ERK phosphorylation and intracellular Ca^{2+} mobilization. This quality allows for the identification of compounds that work as a biased agonist on the MCRs, i.e., compounds that do not stimulate cAMP but stimulate ERK phosphorylation and/or intracellular Ca^{2+} mobilization.

AP1189 is an example of a compound working as a biased agonist on the MC1R and MC3R. The compound has the immune modulating effects comparable to the classical MCR agonist, but since it does not stimulate cAMP, the ability to stimulate melanocytes and thereby skin pigmentation is absent. The latter is potentially a major advantage compared to the classical MCR agonist (and ACTH) where the most undesirable side-effect is the induction of pigmentation following repeated dosing.

AP1189 has shown efficacy in animal models of arthritis and IBD and its ability to treat membranous nephritis is currently being investigated.

Therefore, it is hypothesized that AP1189 may be beneficial as a treatment for RA.

11.3.1 Dose Selection

In this study, the doses of 50 mg and 100 mg AP1189 are selected based on safety, tolerability, and pharmacokinetic results from the PH16028/SynAct-CS001 trial.

Based on in vitro studies in disease models (see section 11.1.3.1.1 in the IB), it is hypothesized that the ideal plasma profile of the compound should induce a peak exposure of AP1189 around 170 ng/ml. As the compound is an agonist, where continued receptor activation could result in the development of tolerance, it is further hypothesized that the trough concentration of the compound, should be kept well below what is needed to induce maximal efficacy. The peak respectively trough concentrations identified in the repeated dose part of the Phase 1 study with AP1189 (PH16028/SynAct-CS001 trial) were during steady conditions as follows:

	C Max (mean +/- SD, N=9)	C Trough (Mean +/- SD, N=9)
50 mg once daily	180 ± 38 ng/ml	46 ± 14 ng/ml
100 mg once daily	427 ± 76 ng/ml	100 ± 25 ng/ml
200 mg once daily	893 ± 198 ng/ml	186 ± 45 ng/ml

Based on the above assumption, the plasma profile following 50 or 100 mg once daily dosing fulfills the assumptions about both C max and C trough with 100 mg inducing a somewhat supratherapeutic exposure. 200 mg, on the other hand, induce plasma levels with plasma concentrations, that based on the above assumption increased the likely hood to induce tolerance.

Consequently, the dose levels to be used in the current study will be 50 and 100 mg.

11.3.2 Benefits and Risks of Participation

The potential benefits of participation, for all subjects in this study, is close monitoring of their medical condition and safety. Those randomized to an active treatment may have a benefit of less pain in affected joints. Subjects randomized to placebo are not expected to obtain any additional benefit, beyond close monitoring of their medical condition and safety.

Based on available non-clinical data, AP1189 appears to be well tolerated at dose levels that induce exposure well above the expected therapeutic level expected to be reached with C_{Max} values around 175 ng/ml.

The toxicology studies showed clinical signs from the gastrointestinal system (reduced appetite, vomiting, and loose stools), the central nervous system (subdued behavior). The clinical signs were most pronounced following *iv* dosing and thereby expected to be associated with high peak concentrations that hardly will be possible to reach following oral dosing. Further, AP1189 at high dose levels induced increased liver weight in rats and minipigs increased kidney weight in minipigs and increased the weight of the ovaries in female rats. Also, hypertrophy/hyperplasia of the thyroid glands was found to be most prominent in the rats. Follow-up studies in minipigs have identified that the treatment-induced increases liver weight was fully reversible following recovery associated with a fully reversible induction of phase I and phase II enzymes. Consequently, the liver findings are to be considered related to increased workload due to fully reversible phase 1 and phase 2 enzyme induction. Likewise, the follicular thyroid hyperplasia in rats most likely is associated with increased hepatic turnover of thyroid hormones.

In Phase 1 clinical trials laboratory parameters of the thyroid gland, such as thyroid-stimulating hormone, as well as liver enzymes, has been evaluated to monitor any effect in humans. No treatment-related effects were identified on thyroid hormones. Regarding liver enzymes, temporal increases up to 1.5x the upper normal value was identified following single dosing at supratherapeutic doses (600 and 800 mg) in a few individuals. Likewise, increases in ALAT was identified following repeat dosing at the 200 ng/ml dose level where 3 out of 9 subjects showed increases above the normal upper level, where one measurement at one occasion reached 3x above the normal upper level. However, 2 out of 3 placebo-treated individuals in the same cohort of subjects did also show increases above the normal upper level. All increased in liver enzymes were without concomitant changes in alkalic phosphatases, and bilirubin, and all values returned to normal at the end of the study. Nevertheless, liver values should be carefully monitored in upcoming clinical trials, and any clinically significant increases in liver enzymes should be carefully assessed and assessed relative to the subjects' pretreatment liver function and co-medication.

Studies on the compound's ability to induce metabolic pathways in primary human hepatocytes have identified AP1189 as a weak inducer of CYP1A2 (also weak compared to omeprazole). Co-medication with compounds metabolized through the CYP1A2 pathway should therefore until further be avoided.

The cardiovascular study in minipigs showed an increase in relative heart rate at the highest dose tested (80 mg/kg). Consequently, even if this study did not reveal any treatment-related effects on blood pressure and ECG parameters, particular attention has been applied to the heart in Phase 1 clinical study. Dedicated tendency analysis on continued ECG assessments was conducted after both single and multiple dosing in Phase 1. The analyses that included testing of changes in ECG following dosing with a positive control knowing to induce QT prolongation showed no treatment effects of AP1189 on ECG or heart rate. Consequently, AP1189 has shown excellent cardiovascular safety.

Based on AUCs, the increase seems to be supra-proportional with an increase of 2.36 for AUC0-t and 2.17 for AUC0-∞ when dose increased by 2. However, in the light of the small sample size (N = 3 or N = 6) this result should be interpreted with caution.

Around 10% of AP1189 dose was excreted unchanged in the urine in 24 h on the dose range 50 - 800 mg. Mean CLr ranged from 2.96 to 4.68 L/h. Consequently, until specific PK evaluation in patients with severe impaired kidney function has been conducted, subjects with stage 5 Chronic Kidney Disease or higher (i.e., eGFR < 30 ml/min) should be excluded in clinical studies.

Up to now, AP1189 has shown an excellent safety profile at all doses tested under the different conditions applied either in single or repeated administration for 14 days. As the maximum tolerated dose was not reached in Phase 1 and as the exposure following repeat dosing of AP1189 given as oral suspension showed that the exposure at the highest dose tested reached up to 5x the expected therapeutic levels, it is considered appropriate and safe to continue dosing in clinical phase 2 at the 50 and 100 mg dose levels.

The effect of food intake on the absorption of AP1189 in the current suspension formulation has not been systematically evaluated. However, it has been shown that the plasma profile of the compound, whether the first meal was served 1 hour or 4 hours post-dosing in the feasting state, is very similar. Further, it has been shown that intake of a glass of apple juice immediately after dosing does not reduce the absorption. Therefore, it is up to the subject whether they would like a glass of juice immediately after dosing.

Consequently, AP1189 present an excellent safety profile allowing its administration to patients at 50 mg or 100 mg doses for 4 weeks.

This study will provide additional safety and efficacy information on the benefit-risk profile of AP1189.

12 OBJECTIVES

12.1 Primary safety Objective

- To compare the safety of AP1189 against placebo by evaluating AEs, SAEs, and laboratory abnormalities.

12.2 Primary efficacy Objective

- Effect of AP1189 vs. placebo in subjects with severe active RA (CDAI > 22), undergoing up-titration with MTX, by showing a change in CDAI from severe (CDAI > 22) to moderate (CDAI ≤ 22) after 4 weeks treatment compared to baseline.

12.3 Secondary efficacy Objectives

To compare the effects of AP1189 against placebo by assessing:

- Proportion of subjects achieving a reduction of more than 10 (ten) swollen and/or tender joints at week 4 compared to baseline
- Proportion of subjects achieving a change in CDAI score at week 4 compared to baseline
    - Proportion of subjects with a 5-point decrease
    - Proportion of subjects with a 10-point decrease
    - Proportion of subjects with a 15-point decrease
- Proportion of subjects achieving a change in value to ≤ 3.2 as measured by DAS28 at week 4 compared to baseline
- Change in subject-reported HAQ-DI at week 4 compared to baseline
- Change in subject-reported fatigue using FACIT-Fatigue at week 4 compared to baseline
- Proportion of subjects achieving American College of Rheumatology (ACR) response assessed by ACR20, ACR50, and ACR70

12.4 Tertiary Efficacy Objectives

Effect of AP1189 compared to placebo at week 4 compared to baseline on inflammatory and collagen destructive biomarkers. The biomarkers include:

- CXCL13
- IL-1β
- IL-6
- IL-10 and TNF-α

12.4.1 Arthroscopy sub-Study

Effect of AP1189 compared to placebo on joint structures and inflammation as assessed by synovial biopsy at baseline and after 4 weeks treatment (only Part 2 at selected sites).

13 SAFETY ENDPOINTS

13.1 Primary Safety Endpoint

The safety of AP1189 against placebo by evaluating adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities.

14 EFFICACY ENDPOINTS

14.1 Primary Efficacy Endpoint

The change in CDAI after 4 weeks of treatment compared to baseline will be evaluated by assessing the following, by treatment group:

- Mean change in CDAI from baseline to week 4
- Proportion of subjects with a change in CDAI score from severe (CDAI > 22) to moderate (CDAI ≤ 22) at week 4 compared to baseline.

14.2 Secondary Efficacy Endpoints

The effects of AP1189 against placebo will be evaluated by assessing the following by treatment group:

- Proportion of subjects achieving a reduction of more than 10 (ten) swollen and/or tender joints (SJC and TJC, summarized) at week 4 compared to baseline
- Proportion of subjects achieving a change in CDAI score at week 4 compared to baseline
    - Proportion of subjects with a 5-point decrease
    - Proportion of subjects with a 10-point decrease
    - Proportion of subjects with a 15-point decrease
- Proportion of subjects achieving a change in DAS28 from DAS28 >3.2 to DAS28 ≤ 3.2 at week 4 compared to baseline
- Change of HAQ-DI at week 4 compared to baseline
- Change of FACIT-Fatigue at week 4 compared to baseline
- Proportion of subjects achieving ACR response assessed by ACR 20, ACR 50, and AC70

14.3 Tertiary Efficacy Endpoints

The effect of AP1189 compared to placebo at week 4 compared to baseline will be further evaluated by assessing the following by treatment group:

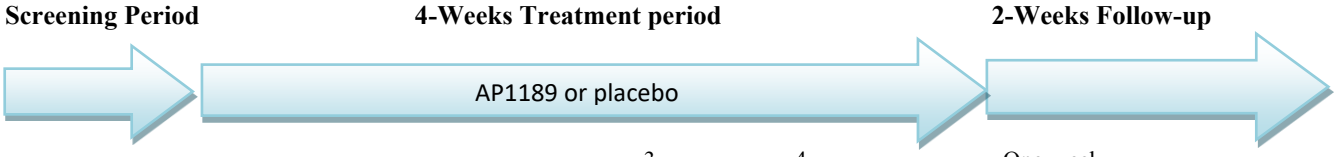
- CXCL13, IL-1β, IL-6, IL-10, and TNF-α
- Synovial biopsy at baseline and after 4 weeks treatment (only Part 2 at selected sites).

15 EXPERIMENTAL PLAN

15.1 Study Design

This study is a multicenter, two-part, randomized, double-blind, placebo-controlled, 4-week study with repeated doses of AP1189. The study population will consist of newly diagnosed subjects with severe active RA (CDAI > 22) who are to start up-titration with MTX. A minimum of 90 subjects are expected to complete the study, plus 45 subjects from Bulgaria and/or Moldova for a sub-study (see Section 15.2). Up to 120 subjects are planned to be enrolled for the main study to account for discontinuation rate, and up to 60 subjects for the sub-study. The rationale for the number of subjects required is outlined in the section on sample size determination. The below Figure 1 shows the general study design.

Figure 1.: General study design (Part 1 and 2)



Screening	Baseline	1. Treatment Visit	2. Treatment visit	3. Treatment Visit	4. Treatment Visit	One-week Post-treatment Visit	Safety Follow-up
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Phone call
Days -14 to -1	Day 0	Day 7 ± 1	Day 14 ± 1	Day 21 ± 1	Day 28 ± 1	Day 35 ± 1	Day 56 ± 2

15.2 Sub-study of subjects from Bulgaria/Moldova

As Bulgaria and Moldova did not participate in Part 1 of the study, a sub-study has been added to investigate the effect in these two countries separately. In addition to analyzing the main study and the sub-study separately, all data will be pooled to investigate the overall effect in all participating countries.

15.3 Part 1 (main study only)

Following a successful screening evaluation, subjects who fulfill the enrollment criteria will be randomized in a 2:1 ratio in group A and B. One group will receive active treatment, and the other group will receive a placebo. Before randomization into group C/D (the same 2:1 ratio between active and placebo), the SC will look at blinded safety data from group A/B.

- Group A (min. 8 subjects): AP1189 dose 50 mg, once daily for 4 weeks (28 days) plus MTX (10-25 mg) weekly
- Group B (min. 4 subjects): placebo for 4 weeks (28 days) plus MTX (10-25 mg) weekly

SC Meeting

- Group C (min. 8 subjects): AP1189 dose 100 mg, once daily for 4 weeks (28 days) plus MTX (10-25 mg) weekly
- Group D (min. 4 subjects): placebo for 4 weeks (28 days) plus MTX (10-25 mg) weekly

15.3.1 Number of Subjects in Part 1

A minimum of 24 subjects is expected to complete Part 1 of the study. About 32 subjects are planned to be enrolled in accounting for discontinuation rate.
The rationale for the number of subjects required is outlined in the section on sample size determination.

15.4 Part 2

All subjects will be randomized into one design only, either design 1, 2, or 3 based on data from the interim analysis:

- Design 1: AP1189 dose 50 mg (min. 44 subjects) or placebo (min. 22 subjects), once daily for 4 weeks (28 days) plus MTX (10-25 mg) weekly
- Design 2: AP1189 dose 100 mg (min. 44 subjects) or placebo (min. 22 subjects), once daily for 4 weeks (28 days) plus MTX (10-25 mg) weekly
- Design 3: Continue with the same doses as in Part 1, in a 1:1:1 ratio (AP1189 50 mg (min. 22 subjects), AP1189 100 mg (min. 22 subjects) or placebo (min. 22 subjects)) plus MTX (10-25 mg) weekly

Following a successful screening evaluation, subjects who fulfill the enrollment criteria will be randomized accordingly.

15.4.1 Number of Subjects in Part 2

A minimum of 66 subjects in the main study is expected to complete Part 2 of the study, and 45 subjects in the sub-study. About 88 subjects are planned to be enrolled in the main study in accounting for discontinuation rate, and about 60 subjects in the sub-study.
The rationale for the number of subjects required is outlined in the section on sample size determination.

15.5 Estimated Study Duration

Total study duration is 18 months, and the study duration for each subject is approximately and up to 10 weeks.

15.6 Number of Investigational Sites

The study is to be conducted at sites in Europe and Moldova.

15.7 Visits during the Study

Subjects will have the following study visits: A Screening Visit (up to 2 weeks prior to baseline), a Baseline Visit (Day 0 visit), four visits during the treatment period (week 1, 2, 3 and 4) and the Follow Up Visit seven days after administration of the last study drug. Investigator or study nurse will make an End of Study (EOS) follow-up call to the subject four weeks after the subject took the last IMP to follow-up on outstanding safety issues (AE/ SAE). The study procedures for each visit are outlined in section 20.

15.8 Steering Committee (SC)

The SC is appointed by the sponsor and comprises of the coordinating investigators in Denmark, Sweden and Norway and a sponsor medical responsible person.
All decisions made by the SC will be documented and signed by its members as per the SC Charter (a specific charter will be developed to define roles and responsibilities).

The SC will review blinded laboratory data from the first min. 12 subjects randomized into group A or B before the next min. 12 subjects in Part I, group C/D can be included and randomized.
The SC will, based on the recommendations from the data monitoring committee (DMC), decide the design for Part 2. The SC will meet ad hoc.

15.9 Data Monitoring Committee (DMC)

The DMC is established by the sponsor and consists of a group of three study independent members: two independent external experts (a rheumatologist and a professor and specialist in hepatology and clinical pharmacology at Bispebjerg hospital), and an independent external statistician. A specific DMC charter will be developed to define roles and responsibilities.

The DMC will review the unblinded data from the interim analysis of the first min. 24 subjects from Part 1. The DMC will recommend a study design for Part 2 to the SC based on these data. All recommendations will be documented and signed by the DMC members, and they will provide a summary of the safety and tolerability data obtained in Part 1 and their design recommendation for Part 2.

The independent external statistician will analyze data for the interim analysis, following the procedure described in the statistical analysis plan and the protocol. The DMC will hereafter meet ad hoc as appropriate.

15.10 Criteria for Choice of Design for Part 2

The criteria for the choice of design 1, 2, or 3 for Part 2 are:

Design 1: AP1189 dose 50 mg (min. 44 subjects) or placebo (min. 22 subjects) plus MTX (10-25 mg) will be applied if:

- The efficacy, evaluated on the number of subjects showing reduced clinical score as defined in the protocol, is higher in the 50 mg group than in the 100 mg group.

- The safety profile of group A and B (50 mg AP1189 or placebo) is superior to the safety profile of group C and D (100 mg AP1189 or placebo).
  The safety evaluation will focus on the number and the severity of the reported AEs and SAEs, on any laboratory findings with particular emphasis on liver and thyroid gland parameters, as well as vital signs.

Design 2: AP1189 dose 100 mg (min. 44 subjects) or placebo (min. 22 subjects) plus MTX (10-25 mg) will be applied if:

- The efficacy, evaluated on the number of subjects showing reduced clinical score as defined in the protocol, is higher in the 100 mg group than in the 50 mg group.

- The safety profile of group C and D (100 mg AP1189 or placebo) is superior or comparable to the safety profile of group A and B (50 mg AP1189 or placebo).
  The safety evaluation will focus on the number and the severity of the reported AEs and SAEs, on any laboratory findings with particular emphasis on liver and thyroid gland parameters, as well as vital signs.

Design 3: Continue with the same doses as in Part 1, in a 1:1:1 ratio (AP1189 50 mg (min. 22 subjects), AP1189 100 mg (min. 22 subjects) or placebo (min. 22 subjects)) plus MTX (10-25 mg) will be applied if:

- The evaluation shows comparable safety profiles and comparable efficacy, evaluated on the number of subjects showing reduced clinical score as defined in the protocol, in the 50 and 100 mg groups.

- The safety evaluation will focus on the number and the severity of the reported AE and SAE, on any laboratory findings with particular emphasis on liver and thyroid gland parameters, as well as vital signs.

15.11 Stopping Rules

In case of occurrence of a serious medical event (e.g., stroke, convulsion, etc.) or any SAE considered as related to the study drug, the DMC could decide to put the study on hold to unblind the study. After that, depending on the results of the unblinding, the study could either be stopped or continued.

16 STUDY POPULATION

The study population will consist of subjects with severe active RA, defined as CDAI > 22, who are about to begin up-titration with MTX.

16.1 Subject Selection Criteria

The study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a subject.

16.2 Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study. The following are requirements for entry into the study.

1. Written informed consent has been obtained prior to initiating any study specific procedures
2. Male and female subjects, 18 to 85 years of age
3. Confirmed diagnosis of RA according to the 2010 ACR/EULAR RA classification criteria
4. Arthritis with joint swelling and tenderness of a minimum of three joints out of 68 joints tested
5. Candidate for MTX treatment
6. Is about to begin treatment with MTX
7. Tested positive for anti-CCP or RF
8. Severe active RA (CDAI > 22) at screening and baseline
9. Negative QFG-IT (Mantoux test can be used if QFG-IT is not possible)
10. Subjects should be able to complete (read and write) the PRO questionnaires
11. Females of child-bearing potential may only participate if using reliable means of contraception (for detailed information see section 17.8) or are post-menopausal (menstrual periods stopped at least 12

months ahead of the enrolment in the trial). Surgically sterilized women at least 6 months prior to screening

12. Females of childbearing potential must have a negative pregnancy test at screening and baseline.

16.3 Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for participation in the study:

1. Participation in any other study involving investigational drug(s) within 4 weeks prior to study entry
2. Major surgery (including joint operation) within 8 weeks prior to screening or planned surgery within 1 month following randomization
3. Rheumatic autoimmune disease other than RA, including SLE, MCTD, scleroderma, polymyositis, or significant systemic involvement secondary to RA (e.g., vasculitis, pulmonary fibrosis or Felty's syndrome). Sjögren syndrome with RA is allowable
4. Functional class IV as defined by the ACR Criteria for Classification of Functional Status in RA or wheelchair/bedbound
5. Prior history of or current inflammatory joint disease other than RA (e.g., gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease)
6. Subjects with fibromyalgia
7. Initiation or change in dose for NSAIDs (including low-dose aspirin and COX-2 inhibitors) within 2 weeks prior to dosing with the IMP
8. Corticosteroids are prohibited within 2 weeks prior to screening (and during the entire treatment period and until the final visit (Visit 7)
9. Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus), or gastrointestinal disease
10. Have prior renal transplant, current renal dialysis, or severe renal insufficiency (determined by a derived glomerular filtration rate (GFR) using Cockcroft Gault formula of ≤30 ml/min/1,73m² calculated by the local lab)
11. Uncontrolled disease states, such as asthma, psoriasis, or inflammatory bowel disease where flares are commonly treated with oral or parenteral corticosteroids
12. Evidence of active malignant disease (except basal cell carcinoma of the skin that has been excised and cured)
13. Pregnant women or nursing (breastfeeding) mothers
14. History of alcohol, drug, or chemical abuse within the 6 months prior to screening
15. Neuropathies or other painful conditions that might interfere with pain evaluation
16. Body weight of >150 kg.

EXCLUSION CRITERIA 17-20 ONLY APPLY FOR SUBJECTS IN NORWAY:

17. Evidence of moderate and/or severe organ dysfunction
18. Abnormal chest x-ray (as per the discretion of the investigator)
19. Evidence of positive hepatitis serology
20. Evidence of peptic ulcer disease

16.4 Recruitment of Subjects

It is intended that potential subjects for this study will be identified amongst patients referred to the clinic for further treatment and diagnosing. Potentially suitable subjects will be approached by the investigating team at the site to ascertain whether they would be interested in participating in the study. Interested subjects will be provided with an information sheet and undergo consenting procedures prior to any other study procedures.

16.4.1 Subject Participation Card

A study participation card will be provided to each subject in the study. The card will indicate that the subject is participating in a clinical trial and give the name and contact details of the sponsor and the investigator/study site. The subjects will be asked to retain this card while they are participating in the trial and show it to any other medical practitioners they consult during this time. They will be advised to contact the investigator/study site if there are any questions.

16.5 Withdrawal

16.5.1 Subject may decide to withdraw

Subjects will be informed that they have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or the institution.

Subjects who prematurely discontinued from the study will not be replaced. The date for premature discontinuation will be recorded in the subject's source documents and electronic Case Report Form (eCRF).

If a subject is discontinued at any time after entering the study, the investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the subject’s rights, as a subject is not obliged to give a reason(s) for withdrawing. The investigator or site personnel should make every effort to contact the subject to assess his or her status and complete the termination page on the eCRF. In the case of subject discontinuation, the procedures described for the End of Study will be applied, where possible.

16.5.2 Discontinuation of Individual Subjects

The investigator may also withdraw a subject from the treatment or the study for any of the following reasons:

- If a subject who does not meet enrolment criteria is inadvertently enrolled
- Enrolment in any other clinical trial with a study drug
- In case of severe worsening of symptoms, the investigator will be able to provide joint injections with corticosteroid as rescue medication. The use of local joint injections will be at the discretion of the investigator. The IMP/placebo treatment will continue as planned
- If the subject, for any reason, requires treatment with another therapeutic agent (rescue medication not included) that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to the introduction of the new agent
- For medical or safety reasons
- If a female becomes pregnant

In case of early subject discontinuation and the reason for discontinuation (if it is known) will be registered in the eCRF and source documentation.

The sponsor can also decide to end the study for safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP. If the sponsor decides to stop the study, the subject should be informed of the reason hereof.

17 TREATMENT PLAN AND PROCEDURES

17.1 Subject Identification

Each subject who signs the informed consent will be assigned a unique subject number (01-1001 site 1, 02-1001 etc.), which will be used as the subject's identification in the eCRF and on all source documentation throughout the study. The screened subjects will be consecutively numbered, and the first available number, as listed in the eCRF, will be used. In the case of re-screening, a new screening number will be allocated. Subjects who are assigned a subject number but fails the randomization will be registered as a screen failure on the screening list and in the eCRF.

17.2 Randomization and Treatment Assignment

Following a successful screening evaluation, eligible subjects will be randomized into the study.

Each subject will be assigned a unique randomization number in ascending order, based on a list provided by HB Medical, and assigned a protocol specified drug treatment. Randomization numbers should be assigned according to the list and should not be omitted or reused.

An external statistician will prepare the randomization list and emergency code envelopes. The randomization list will be kept strictly confidential, filed securely by HB Medical (or designee), and accessible only to authorized persons per HB Medical's Standard Operating Procedures (SOPs) until the time of unblinding. A copy of the list is sent to PharmaLex Denmark, who is handling the pharmacovigilance.

The study treatment will be unknown to the Clinical Research Organization (CRO) and sponsor personnel associated with the study, all subjects, the investigator, and all site personnel except for the unblinded pharmacist(s) and personnel at HB Medical and the unblinded statistician responsible for preparing the randomization list.

18 INVESTIGATIONAL PRODUCT(S)

The individual study drug information is presented in the below tables.

Table 1, Test Treatment

Name	AP1189
Dosage strength	50 mg, 100 mg
Formulation	Powder
Route of	Oral
Supplier	SynAct Pharma

Table 2, Reference Treatment

Name	Placebo
Dosage strength	0 mg
Formulation	Powder
Route of	Oral
Supplier	SynAct Pharma

A description of the pharmaceutical properties and composition of the formulation of AP1189 is provided in the IB.

18.1 Description of AP1189 Investigational Product

18.1.1 Nomenclature

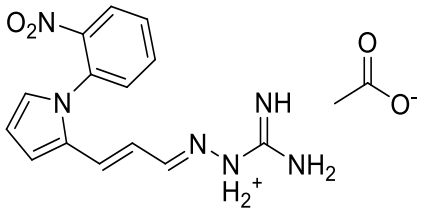
IUPAC: *E-N*-[*trans*-3-{1-(2-nitrophenyl)-1H-pyrrole-2-yl}-allylideneamino] guanidinium acetate

Proprietary: AP1189

18.1.2 Drug Substance

The substance is an acetic acid salt that appears as an odorless, yellow solid.

- **Structural formula**



- **Molecular formula:** $C_{16}H_{18}N_6O_4$

18.1.3 Basic physical and chemical Characteristics

The molecular weight is 358.35 for the salt and 298.30 for the free base.

18.2 Packaging and Labeling

The sponsor (or designee) will provide HB Medical with study drug. IMP/placebo will be delivered the sites in bottles with screw caps and labeled following all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

The label on the box containing the bottles with IMP will include the following information:

- Study number
- AP1189/ placebo powder in bottle
- Batch number
- Randomization number
- Expiry date
- Storage conditions
- Name and phone number of the responsible investigator

- Sponsor name and address
- For clinical trial use only
- Keep out of reach of children

The label on the bottles containing AP1189/placebo, which is to be dispensed to subjects, will include the following information:

- Study number
- AP1189/ placebo powder in bottle
- Randomization number
- Batch number
- Storage conditions
- Name and phone number of the responsible investigator
- Sponsor name and address
- For clinical trial use only
- Keep out of reach of children

Labels on the box and the bottles will be in the local language.

18.3 Drug Supplies

After receipt of all required documentation, including written approval from the IEC/IRB and CA, HB Medical will supply sufficient study drug/ placebo for the clinical sites to conduct the study, as appropriate.

18.3.1 Drug Accountability

The investigator at each site must maintain adequate records documenting the receipt, use, loss, or other disposition of drug supplies.

The site pharmacist/study nurse (as appropriate per country) will verify that study drug supplies are received intact and in the correct quantities which will be documented by signing and dating the Proof of Receipt. The site pharmacist/study nurse will also sign and date a Proof of Receipt for the corresponding code envelopes. An accurate (running) inventory of study drug will be kept by the site and will include the batch number, date of receipt, subject number, date, and initials of the person who dispense the drug, and finally the date and amount of study drug each subject return to the site. A sample of the Drug Accountability Form, following instructions provided by the monitor, will also be provided to the site pharmacist/study nurse. Accountability of the study drug will be performed and verified by the monitor throughout the study duration.

All unused IMP/placebo must be registered, accounted for, and returned to HB Medical or destroyed per instructions from SynAct Pharma and according to local regulations. The investigator, subinvestigator(s), and/or site pharmacist/study nurse agree not to supply study medication to any persons not enrolled in the study.

18.3.2 Storage and Handling

The IMP/placebo will be stored in a secure limited access area in accordance with required storage conditions. The study pharmacist/investigator at each site will be responsible for the correct storage and handling of the study products.

Both AP1189 and placebo should be stored at room temperature between +15°C and 25°C. All study drug must be protected from light and moisture. They should not be refrigerated or frozen.

18.4 Administration and handling of Study Drug

The study drug will be dispensed four times during a subject's participation in Part 1 and Part 2 respectively; at the Baseline Visit, visit 2, visit 3 and at visit 4. The study drug will be in a box with 8 bottles (study drug for one week's use) containing powder of either AP1189/placebo, a funnel, and a measuring cup.

The subject adds 50 ml of tap water to the powder in the bottle, shakes well for about 1 minute allowing all powder to dissolve and then immediately drink the solution. The subject must rinse the bottle two times with 50 ml water to ensure ingesting all the medicine in the bottle. Between each rinse, the content of the bottle is drunk. Each subject will use one bottle daily during the treatment period.

The subjects will be instructed to take the suspension once daily in the morning about an hour before breakfast during the treatment period. It is up to the subject whether they would like to drink a glass of apple juice immediately after dosing. On the visit days, the medication should first be taken after blood sampling has been done.

At the Baseline Visit, the subject will receive a diary to make daily records of what time the treatment is taken.

The investigator or her/his designee is responsible for explaining the correct use of the study drug and the diary to each subject, and the subjects will receive a written instruction too.

Subjects will be instructed to return empty bottles, unopened bottles, and the diary at each visit.

The effect of food intake on the absorption of AP1189 in the current suspension formulation has not been systematically evaluated. However, it has been shown that the plasma profile of the compound, whether the first meal was served 1 hour or 4 hours post-dosing in the fasting state, is very similar. Further, it has been shown that intake of a glass of apple juice immediately after dosing does not reduce the absorption.

18.5 Blinding

18.5.1 Blinding of Investigational Product

This study is conducted under double-blind conditions primarily to minimize bias in the reporting, collection, and initial assessment of data.

The investigator, study personnel, as well as sponsor personnel involved in the conduct of the study, will be blinded to the study medication. Except in the case of emergency, the study randomization codes will not be available to the above personnel until after the completion of the study and final data review.

Emergency code envelopes, which each investigational site will receive every time they receive a new batch of IMP, will be kept in a secure environment at the individual study site. A code, which reveals the treatment

allocated for a specific subject, may in case of emergency be opened during the study if the choice of treatment depends upon it.

18.5.2 Breaking the Blind

The study blind can be broken if, in the opinion of the investigator, it is in the subject's best interest to know the study drug assignment. SynAct Pharma must be notified before breaking the blind unless identification of the study drug is required for emergency therapeutic measures. If an emergency therapeutic measure is necessary which warranted breaking of the blind, SynAct Pharma must be notified within 24 hours of the blind being broken. The date and reason for blind breaking must be recorded in source documentation.

19 PRIOR AND CONCOMITANT MEDICATION

Prior medications and therapies are taken within 4 weeks prior to the Screening Visit. Concomitant medications are those medications, other than study drug, taken after the Screening Visit. Both prior medications, as well as concomitant medications, will be recorded in the eCRF by generic name.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving up to 4 weeks prior to screening or receives at any time during the study will to be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route, and frequency.

19.1 Permitted Medicines

Permitted medications are any medications required per the medical history and not explicitly prohibited by the protocol during the trial. These standard of care medications are part of the subject's previous treatment and will therefore not be provided by the sponsor. Any such medications prescribed or used should be recorded in the eCRF.

19.1.1 Methotrexate (MTX)

All subjects should follow the local guideline for each hospital and/or country for starting treatment with MTX and continue MTX treatment throughout their participation in the study. MTX is not provided by the sponsor, as it is not background treatment but part of the patients' regular treatment.

19.1.1.1 MTX Treatment Instruction in Case of Elevation in Liver Enzymes

It is recommended with more frequent blood test in case of elevation of liver enzymes.

Transaminase Increase:

Laboratory Value	Action
ALT and/or AST increases up to > 1 to ≤ 3 x Upper Limit of Normal (ULN) And bilirubin is within the normal range	IMP and MTX remains unchanged. It is recommended with more frequent blood test in case of elevation of liver enzymes.

Laboratory Value	Action
ALT and/or AST increases > 3 to ≤ 5 x ULN	Pause IMP dosing until ALT and/or AST < 3 x ULN and follow recommendations above for > 1 to < 3 x ULN
And bilirubin is within the normal range	Upon normalization of ALT and/or AST, IMP resumes For persistent increases > 3 x ULN, discontinue IMP
ALT and/or AST > 5 x ULN	MTX and IMP discontinue
Bilirubin > normal range	MTX and IMP treatment discontinue

19.1.2 Folic Acid

It is possible that AEs commonly associated with MTX treatment will occur. To minimize MTX toxicity, all subjects treated with MTX should be on folic acid or equivalent at a dose of at least 5 mg/week according to local guidelines and at the discretion of the investigator. Folic acid can either be given as a single dose weekly or be divided into daily doses to achieve at least 5 mg folic acid per week. It is the investigator's decision as to which dosing regimen is used.

19.1.3 Oral Corticosteroids

Oral corticosteroids are prohibited within 2 weeks prior to screening and during the entire treatment period and until the final visit (Visit 7). Refer to section 19.2 for treatment of asthma patients.

19.1.4 Nonsteroidal anti-inflammatory Drugs (NSAID)

Subjects may be treated with NSAIDs throughout the study. The choice and dose of NSAID used are at the discretion of the investigator, and the dose must be stable throughout the study. Adjustments to the dose or a change in NSAID may only be performed for safety reasons, and this change must be documented in the eCRF.

19.1.5 Non-NSAID Analgesics

Analgesics may be used for pain as required. However, subjects should not take analgesics within 12 hours prior to a visit where clinical efficacy assessments are performed and recorded. Adjustments to the analgesic regimen may only be made for safety reasons, but any change must be documented in the eCRF.

19.2 Prohibited Medicines

The following medications and therapies are not permitted during the trial and would require discontinuation of trial treatment:

- Oral, intramuscular, intravenous or intra-articular corticosteroids (permitted after week 5). (Asthma patients on stable prophylactic treatment are allowed to use an inhalation spray containing adrenocortical hormone. Furthermore, Beta-2 stimulating inhalants with short-term effects (SABA) are allowed for an asthma attack to an otherwise well-controlled asthma patient in the opinion of the investigator)
- Biologic therapies for RA
- Intravenous immunoglobulin therapy and/or plasmapheresis
- New therapies for RA should not be initiated during the trial. Initiation of any new immunosuppressant or immunomodulatory therapy would be considered a treatment failure and should result in withdrawal of the subject from the IMP.

As a signal for CYP1A2 induction has been observed at 10 µM in a study with human hepatocyte the following CYP1A2 substrates are also prohibited:

- Alosetron
- Clozapine
- Flutamide
- Frovatriptan
- Melatonin
- Mexiletine
- mirtazapine
- Olanzapine
- Ramelteon
- Rasagiline
- Ropinirole
- Tacrine
- Theophylline
- Tizanidine
- Triamterene
- zolmitriptan

19.3 Rescue Treatment

In case of severe worsening of symptoms, the investigator will be able to provide joint injections with corticosteroid as rescue medication. The use of local joint injections will be at the discretion of the investigator. The IMP/placebo treatment will continue as planned.

19.4 Treatment Compliance

Subject's compliance with study medication will be assessed at each visit. Every attempt will be made to select subjects who can understand and comply with instructions. Noncompliant subjects may be discontinued from the study at the discretion of the investigator. The sites will maintain drug accountability records and record the time and day of drug administration.

20 SCHEDULE OF VISITS

The schedule of visits and main procedures at each visit are summarized in the study flowchart below and are identical for Part 1 and Part 2.

Table 3: Study Flow Chart

Visit	1 Screening	2 Baseline	3	4	5	6	7	8 EOS Safety follow-up call[2]
Week	-2	0	1	2	3	4	5	8
Visit Window	-14 to -1d	Day 0	±1d	±1d	±1d	±1d	±1d	±3d
Informed consent	X							
Randomization		X						
Demographics	X							
Medical and surgical history	X							
Inclusion/Exclusion criteria	X	X						
Pregnancy test (serum β-HCG)	X							
Pregnancy test (dipstick)		X	X	X	X	X	X	
TB test[1]	X							
Physical examination	X						X	
Vital signs	X	X	X	X	X	X	X	
Height and weight[3]	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	
Concomitant therapy	X	X	X	X	X	X	X	
Electrocardiogram (ECG)	X	X	X	X	X	X	X	
X-ray of chest, hands, and feet	X							
SJC and TJC	X	X		X		X	X	
CDAI	X	X		X		X	X	
Investigator Global VAS[5]	X	X		X		X	X	
Patient Global VAS	X	X		X		X	X	
Patient Pain VAS	X	X		X		X	X	
FACIT-Fatigue		X		X		X	X	
DAS28		X		X		X	X	
HAQ-DI (Health Assessment Questionnaire-Disability Index)		X		X		X	X	
SAEs/AEs		X	X	X	X	X	X	X
Blood samples (biochemistry and TSH, T3, and T4)	X	X	X	X	X	X	X	
Blood samples (hematology)	X	X		X		X	X	
Blood sample (MC1R genotype analysis)[7]		X						
HBsAg, HBV antibody & HCV antibody[4]	X							
PK (exposure)			X	X	X	X		
C-Reactive Protein (CRP)	X	X		X		X	X	
RF or anti-CCP	X							
Cytokines[6]		X		X		X		
Urinalysis	X						X	
Dispensing of IMP		X	X	X	X			
Accountability of returned IMP			X	X	X	X		

1: QFG-IT (Mantoux test can be used if QFG-IT is not possible)

2: WD: Withdrawal. In case of prematurely subject withdrawal, the final visit should occur 7 days after the last IMP. Four weeks after the last IMP the subject will have a final safety follow-up call (EOS).

3: Height only at screening

4: Hepatitis B surface antigen (HBsAg), Hepatitis B virus (HBV), Hepatitis C virus (HCV)

5: Visual Analog Scale (VAS)

6: CXCL13, IL-1β, IL-6, IL-10, and TNF-α

7: At baseline or any other visit after randomization

20.1 Visits

20.1.1 Visit 1, Screening (up to 14 days prior to the Baseline Visit)

The purpose of the screening visit is to inform the subject about the trial and to verify that the potentially eligible subject fulfills the inclusion criteria for the trial and do not meet any exclusion criteria. The screening visit should be performed within 14 days prior to the Baseline Visit. The informed consent must be signed prior to any screening assessments.

The following assessments will be performed:

- Informed consent
- Demographics
- Medical and surgical history
- Inclusion/exclusion criteria
- TB test (QFG-IT (Mantoux test can be used if QFG-IT is not possible))
- Physical examination
- Vital signs (supine blood pressure (BP) and heart rate)
- Body measurements (height and weight)
- Concomitant medication
- Concomitant therapy
- 12-lead ECG
- X-ray of chest, hands, and feet
- Blood samples (haematology, biochemistry and TSH, T3, and T4)
- Pregnancy test (serum)
- HBsAg, HBV antibody & HCV antibody
- Urinalysis (dipstick)
- RF or Anti-CCP
- CRP
- SJC and TJC
- CDAI
- Investigator Global VAS
- Patient Global VAS

- Patient Pain VAS

20.1.2 Visit 2, the Baseline Visit (Day 0)

The subject will come back to the hospital for the Baseline Visit. Inclusion and exclusion criteria will be confirmed. If the subject is still eligible for participation, the subject will be randomized. The following assessments will be performed:

- Check of inclusion/exclusion criteria
- Vital signs (supine BP and heart rate)
- Changes in concomitant medication
- Changes in concomitant therapy
- 12-lead ECG
- Blood samples (hematology, MC1R genotype analysis*, biochemistry and TSH, T3, and T4)
- CRP
- Cytokines
- Pregnancy dipstick test
- Body measurements (weight)
- Adverse event recording
- SJC and TJC
- CDAI
- Investigator Global VAS
- Patient Global VAS
- Patient Pain VAS
- FACIT-Fatigue
- DAS28
- HAQ-DI
- Randomization
- Dispensing of IMP

* At baseline or any other visit after randomization

20.1.3 Visit 3, 1. Week treatment Visit

The 1. Week Treatment Visit, 7 days (±1 day) after the Baseline Visit. The following assessments will be performed:

- PK blood sample
- Blood samples (biochemistry and TSH, T3, and T4)
- Changes in concomitant medication
- Changes in concomitant therapy

- 12-lead ECG
- Pregnancy dipstick test
- Body measurements (weight)
- Adverse event recording
- Accountability of returned IMP and dispensing of new IMP

20.1.4 Visit 4, 2. Week treatment Visit

The 2. Week Treatment Visit, 14 days (±1 day) after the Baseline Visit. The following assessments will be performed:

- PK blood sample
- Vital signs (supine BP and heart rate)
- Changes in concomitant medication
- Changes in concomitant therapy
- 12-lead ECG
- Blood samples (hematology, biochemistry and TSH, T3, and T4)
- Cytokines
- CRP
- Pregnancy dipstick test
- Body measurements (weight)
- Adverse event recording
- SJC and TJC
- CDAI
- Investigator Global VAS
- Patient Global VAS
- Patient Pain VAS
- FACIT-Fatigue
- DAS28
- Accountability of returned IMP and dispensing of new IMP

20.1.5 Visit 5, 3. Week treatment Visit

The 3. Week Treatment Visit, 21 days (±1 day) after the Baseline Visit. The following assessments will be performed:

- PK blood sample
- Blood samples (biochemistry and TSH, T3, and T4)
- Changes in concomitant medication
- Changes in concomitant therapy

- 12-lead ECG
- Pregnancy dipstick test
- Body measurements (weight)
- Adverse event recording
- Accountability of returned IMP and dispensing of new IMP

20.1.6 Visit 6, 4. Week treatment Visit

The 4. Week Treatment Visit 28 days (±1 day) after the Baseline Visit. The following assessments will be performed:

- PK blood sample
- Vital signs (supine BP and heart rate)
- Changes in concomitant medication
- Changes in concomitant therapy
- 12-lead ECG
- Blood samples (hematology, biochemistry and TSH, T3, and T4)
- CRP
- Cytokines
- Pregnancy dipstick test
- Body measurements (weight)
- Adverse event recording
- SJC and TJC
- CDAI
- Investigator Global VAS
- Patient Global VAS
- Patient Pain VAS
- FACIT-Fatigue
- DAS28
- HAQ-DI
- Accountability of returned IMP

20.1.7 Visit 7, One-week post-treatment

The subject will return to the hospital for a final visit, 7 (±2 days) days after the last IMP has been taken. The following assessments will be performed:

- Pregnancy dipstick test
- Urinalysis (dipstick)
- Blood samples (hematology, biochemistry and TSH, T3, and T4)

- Vital signs (supine BP and heart rate)
- CRP
- Physical examination
- Body measurements (weight)
- Adverse event recording
- Changes in concomitant medication
- Changes in concomitant therapy
- 12-lead ECG
- SJC and TJC
- CDAI
- Investigator Global VAS
- Patient Global VAS
- Patient Pain VAS
- FACIT-Fatigue
- DAS28
- HAQ-DI

20.1.8 Final safety Follow-up Call and EOS

Investigator or study nurse will call the subject 4 weeks after the subject took the last IMP to follow-up on outstanding safety issues (AE/SAE).

21 ASSESSMENTS, PROCEDURES, AND EXAMINATIONS

Subjects must provide written informed consent before any study-related procedures are performed.

Subject-related events and activities including specific instructions, procedures, concomitant medications, dispensing of study drug, and descriptions of AEs should be recorded in the appropriate source documents and the eCRF.

The schedule of assessments is provided in a study flow chart (Table 3) and is listed in Section 205. Unless otherwise specified, the investigator or accredited study personnel will perform all assessments.

Extra visits, examinations, tests, and interventions can be performed at any time if clinically indicated, as judged by the investigator.

21.1 Safety Assessments

21.1.1 Medical History

A complete medical (and surgical) history of each subject will be collected and documented during screening to determine the subject's eligibility for the trial. The medical history will include, but may not be limited to, prior and current concomitant disease and treatments, including all previous and current therapies for RA.

Relevant medical history will be recorded in the eCRF and includes diagnosis and assessments of any current medical condition and concurrent health conditions.

21.1.2 Prior and Concomitant Medication

Prior medications/therapies will be reported if taken up to 4 weeks prior to the Screening Visit. Concomitant medications/therapies, herbal medication, and over-the-counter medication will be reported at every visit throughout the trial.

21.1.3 Pregnancy Test

For all females of childbearing potential, a serum pregnancy test will be performed at screening and at all the following visits the pregnancy test will be a urine dipstick test. In the event of pregnancy, the subject is not allowed to receive further study treatment and must be withdrawn from the study. The pregnancy must be reported to the sponsor on a Pregnancy form and followed until the end of pregnancy.

21.1.4 Physical Examination

A full physical examination (including examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, musculoskeletal, cardiovascular, nervous systems, and joints) will be carried out by a physician at screening and at the final visit (Visit 7) or early withdrawal. Any clinically significant abnormalities at screening will be noted on the medical history pages of the eCRF. During the study, if in the opinion of the investigator there are any clinically significant changes in the physical examination findings (abnormalities), they will be recorded as AEs.

21.1.5 Height and Weight

Subject height will be measured at the Screening Visit, while weight will be assessed at all visits except at the visit 8 (EOS/Safety follow-up call).

21.1.6 Vital Signs

Vital signs will be collected for evaluation by the investigator. Reference values for the vital signs are presented in the table below. If any value is outside the reference range, the measurement will be repeated at the investigator's discretion, and the final measurement will be reported in the eCRF.

Table 4, Reference values for vital signs

Vital Sign Parameter	Range
Systolic blood pressure	90–140 mm Hg
Diastolic blood pressure	60–90 mm Hg
Heart rate (resting)	50–100 beats per minute (bpm)
Respiratory rate	12–20 breaths per minute

All vital sign values will be evaluated for clinically notable results as defined in Table 5, Any subject with a clinically notable vital sign abnormality will be immediately evaluated by qualified personnel to ensure that any required acute medical intervention or other appropriate supportive medical care is provided. All vital sign abnormalities, including clinically notable vital sign abnormalities, will be evaluated using appropriate medical

judgment to determine whether they represent AEs. Vital sign abnormalities that require medical intervention (beyond confirmatory vital sign collection) are to be regarded as AEs. Vital signs will be assessed at all visits.

Table 5, Criteria used to identify clinically notable vital sign abnormalities

Vital Sign Parameter	Value
Systolic blood pressure	≥ 160 mm Hg or < 90 mm Hg
Diastolic blood pressure	≥ 105 mm Hg or ≤ 50 mm Hg
Heart rate	≥ 120 bpm or < 40 bpm
Respiratory rate	< 12 breaths per minute or > 20 breaths per minute

21.1.6.1 Blood pressure, Heart, and Respiratory Rate

Blood pressure and pulse rate will be measured on the non-dominant arm after 5 minutes of supine rest. Blood pressure will be recorded in mmHg, heart rate will be measured in bpm and respiratory rate in breaths per minutes.

21.1.7 Lead Electrocardiographic Evaluation

A twelve (12) lead ECGs will be obtained on all subjects at every visit throughout the trial. The ECG should be performed after the subject has rested quietly for at least 10 minutes.

The following ECG parameters will be obtained from the digital 12-lead ECG recordings: rhythm, heart rate (as measured by RR interval), PR interval, QRS duration, and QT interval. The corrected QT interval (QTcF) will be calculated using Fridericia's formula ($QTc=QT/\sqrt[3]{RR}$)[43] or by using CliniCalc: (https://www.clinigate.com/clinicalc/corrected-qt-interval-qtc.php)

The investigator must evaluate all ECGs as normal/abnormal and if abnormal as clinically significant or not clinically significant. The printout of the ECG should be signed and dated. The overall evaluation (normal/abnormal) will be recorded on the eCRF, and if abnormal, the specific abnormality will be recorded too.

Each print-out must include the following information: trial number, subject's screening number, date of birth, and date and time of recording. All reference to the subject's name and/or social security number must be erased from the print-out so that only the subject's screening number is used as identification.

21.1.8 X-ray

A chest x-ray (only at the Screening Visit) will be used to reveal active current or history of tuberculosis and atypical mycobacterial disease, clinically significant abnormalities on chest x-ray as determined by the investigator.

X-ray of hands and feet (only at the Screening Visit): radiographic changes typical of RA on posteroanterior hand and wrist x-rays.

If the subject has a chest x-ray and/or x-ray of hands and feet that are no older than 6 months the x-rays can be used for the evaluation.

The average radiation dose for adults is 60 microsievert (µSv) per x-ray image, which is a very shallow dose. In comparison, the average background radiation (i.e., the average radiation that an individual is exposed to per year from natural background radiation sources) is 1000 µSv. The radiation dose that a subject is exposed to is thus evaluated to be safe. Furthermore, the additional information, which such images can provide about radiographic changes typical for rheumatoid arthritis, is anticipated as valuable knowledge for the project.

21.1.9 Laboratory Assessments

The study sites will use local laboratories to perform standard hematology, biochemistry, and urine analyzes. Laboratory results will be evaluated by the investigator for inclusion and exclusion criteria. Also, the investigator will assess whether any values reflect AEs and if so, report them as described in section 18.
The latest updated reference ranges from the local laboratory will be used to identify subjects with clinically notable laboratory values.

21.1.9.1 Hematology

Hemoglobin, white blood cell (WBC) count (total and differential: leukocytes, neutrophils, eosinophils, basophils, lymphocytes, monocytes), red blood cells (RBC), thrombocytes and hemoglobin A1c (HbA1C). The hematology blood samples will be taken at screening, baseline, after 2 weeks and 4 weeks treatment and Visit 7.

21.1.9.2 MC1R genotype analysis

The human melanocortin receptor type 1 (MC1R) is a highly polymorphic gene. It is known that some receptor variants are associated with loss of function when characterized by the receptor's ability to induce cAMP accumulation. There is evidence that the loss of function is restricted to the cAMP pathway, i.e., the ability to stimulate the ERK phosphorylation pathway, the pathway stimulated by AP1189, for most receptor variants are preserved.

At baseline or any other visit after randomization, a blood sample will be taken once to identify the MC1R variant in randomized patients.

The blood sample is stored at -80 ° in a research biobank until shipment and subsequent analysis at Statens Serum Institut (SSI). The genotype sequencing method is used in the blood sample analysis, meaning that only the gene variations that have to do with the melanocortin receptor are examined.

The company Genetelligence is responsible for the interpretation of the genetic tests, and the results are only used in the above study.

All blood samples will be destroyed after analysis, and no samples will be saved for future research.

21.1.9.3 Biochemistry

Sodium, potassium, chloride, calcium, glucose, creatinine, urea, albumin, unconjugated and total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and INR. The biochemistry blood samples will be taken at all visits. A serum β-HCG pregnancy test will be taken at screening (dipstick pregnancy test at all other visits).

21.1.9.4 Thyroid function

Thyroxine (T4) total or free, triiodothyronine (T3) total or free, and the thyroid-stimulating hormone (TSH). Blood samples for measuring the thyroid function will be taken at all visits.

21.1.9.5 Urinalysis

A dipstick urine test for blood, protein, and glucose will be performed at the site at the Screening Visit and Visit 7. If any of the results are abnormal and clinically significant, a urine sample will, at the discretion of the investigator, be sent for urine culture at the local laboratory.

21.1.9.6 Serology

RF or anti-CCP, HBsAg, HBV antibody and HCV antibody (only at screening).

RF is an antibody that is detectable in the blood of approximately 80% of adults with RA.

CRP is an acute phase reactant, a protein made by the liver and released into the blood within a few hours after tissue injury, the start of an infection, or other cause of inflammation. The CRP will most often be increased by inflammation. One of the aims of treatment is to reduce the CRP to normal levels. CRP will be measured at screening, baseline, after 2 weeks and 4 weeks treatment and at Visit 7.

21.1.9.7 Safety (AE and SAE)

Safety measures (AEs, SAEs, including laboratory abnormalities) will be registered during the whole study duration.

21.2 Safety Assessments (Sub-study, only Part 2)

The arthroscopy sub-study in Part 2 (only at selected sites), will assess the effect of 4 weeks treatment with AP1189/placebo compared to baseline by examining synovial fluid: (evaluating the change in the percentage of polymorphs, monocytes, and lymphocytes in synovial fluid).

In RA the immunohistological features of synovial inflammation change as the clinical manifestations change in response to conventional disease-modifying antirheumatic drugs, pulse methylprednisolone, or intra-articular glucocorticoids[45, 45, 46, 47, 48, 49, 50, 51]. These observations from many clinicopathological research protocols have provided compelling evidence to support the inclusion of synovial biopsy and tissue analysis in studies of the cause, pathogenesis, prognosis, and effects of treatment[52].

21.3 Efficacy Assessments

The following tests and procedures have been selected to evaluate the efficacy of AP1189 and to describe the clinical improvement in subjects with RA. The tests and procedures will be performed according to the Study Flow Chart in section 18, Table 3.

21.3.1 Swollen Joint Count (SJC) and Tender Joint Count (TJC)

An assessment of 66 joints for swelling and 68 joints for tenderness will be made at screening, baseline, after 2 weeks and 4 weeks treatment and Visit 7. Joints will be assessed and classified as swollen/not swollen and tender/not tender by pressure and joint manipulation on physical examination. The subject will be asked for pain sensations on these manipulations and watched for spontaneous pain reactions. Any positive response to pressure, movement, or both will then be categorized as tender-versus-nontender. Swelling is defined as

palpable fluctuating synovitis of the joint. Swelling secondary to osteoarthrosis will be assessed as not swollen unless there is unmistakable fluctuation.
Joint assessments of one particular subject should be performed by the same assessor (if at all possible) throughout the trial to minimize inter-observer variation.

21.3.2 Clinical Disease Activity Index (CDAI)

The CDAI is a useful clinical composite score for following patients with RA.
Descriptive changes in CDAI where CDAI = SJC (28) + TJC (28) + PGA + IGA

- SJC (28): Swollen 28-Joint Count (shoulders, elbows, wrists, MCPs, PIPs including thumb IP, knees)
- TJC (28): Tender 28-Joint Count (shoulders, elbows, wrists, MCPs, PIPs including thumb IP, knees)
- PGA: Patient Global Disease Activity (patient's self-assessment of overall RA disease activity on a scale 0-100 where 100 is maximal activity)
- IGA: Physician's Global Disease Activity (evaluator's assessment of the subject's overall RA disease activity on a scale 0-100 where 100 is maximal activity)

The CDAI will be scored at screening, baseline, after 2 weeks and 4 weeks treatment and at Visit 7.

21.3.3 Disease Activity Score 28 (DAS28)

The DAS28 is a combined index for measuring disease activity in RA. The index includes swollen and tender joint counts, CRP, and general health status. In this trial CRP will be used to calculate the DAS28 score. The index is calculated using the following formula:

DAS28-CRP(4) = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*ln(CRP+1) + 0.014*GH + 0.96

Where, TJC = tender joint count on 28 joints, SJC = swollen joint count on 28 joints, ln = natural log, CRP = C-reactive Protein, and GH = general health, i.e., patient's global assessment of disease activity (100-mm VAS).

The DAS28 provides an absolute indication of RA disease activity on a scale of 0.49 to 9.07

- A DAS28 value >5.1 corresponds to a high disease activity
- A DAS28 value between 3.2 and 5.1 corresponds to a moderate disease activity
- A DAS28 value between 2.6 and 3.2 corresponds to a low disease activity
- A DAS28 value < 2.6 corresponds to remission

Compared to an initial value the disease activity of the subject can be classified as follows:

Current DAS28		**DAS28 decrease from initial value**		
		> 1.2	**> 0.6 but ≤ 1.2**	**≤ 0.6**
≤ 3.2	Inactive	Good improvement	Moderate improvement	No improvement
>3.2 but ≤ 5.1	Moderate	Moderate improvement	Moderate improvement	No improvement
> 5.1	Very active	Moderate improvement	No improvement	No improvement

The DAS28 will be scored at baseline, after 2 weeks and 4 weeks treatment and at Visit 7.

21.3.4 Physician's Global Assessment of Disease Activity VAS ("Investigator Global VAS")

The physician's assessment of the subject's current disease activity on a 100 mm horizontal VAS. The extreme left end of the line should be described as "no disease activity" (symptom-free and no arthritis symptoms) and the extreme right end as "maximum disease activity." The efficacy assessor should complete this. Investigator Global VAS will be measured at screening, baseline, after 2 weeks and 4 weeks treatment and at Visit 7.

21.3.5 Patient's Global Assessment of Disease Activity VAS ("Patient Global VAS")

The subject's overall assessment of their current disease activity on a 100 mm horizontal VAS. The extreme left end of the line should be described as "no disease activity" symptom-free and no arthritis symptoms) and the extreme right end as "maximum disease activity" (maximum arthritis disease activity). Patient Global VAS will be measures at screening, baseline, after 2 weeks and 4 weeks treatment and at Visit 7.

21.3.6 Patient's Assessment of Pain VAS ("Patient Pain VAS")

The subject's assessment of his/her current level of pain on a 100 mm horizontal VAS. The extreme left end of the line should be described as "no pain" and the extreme right end as "unbearable pain." Patient Pain VAS will be measured at screening, baseline, after 2 weeks and 4 weeks treatment and at Visit 7.

21.3.7 Quality of Life and Physical Function

21.3.7.1 Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)

The FACIT-Fatigue assessment is a 13-item questionnaire with subjects scoring each item on a 5-point scale. The assessment was originally developed for chronic illnesses and is now validated for patients with RA. FACIT-Fatigue will be scored at baseline, after 2 weeks and 4 weeks treatment and at Visit 7.

21.3.7.2 Health Assessment Questionnaire – Disability Index (HAQ-DI)

HAQ-DI is a validated tool to evaluate physical function. It consists of 20 questions referring to 8 component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. HAQ-DI will be scored at baseline, after 2 weeks and 4 weeks treatment and at Visit 7.

21.3.8 American College of Rheumatology Response Rates

The ACR (American College of Rheumatology) Criteria is a standard criterion to measure the effectiveness of various arthritis medications or treatments in clinical trials for RA.

The ACR response rates ACR20, ACR50, and ACR70 are defined as ≥20%, ≥50% and ≥70% improvement, respectively, in swollen and tender joint counts (SJC/TJC) and 3 of the following 5 assessments: Patient's Global Assessment of Disease Activity (see above), Physician's Global Assessment of Disease Activity (see above), Patient's Assessment of Pain (see above), Health Assessment Questionnaire (HAQ-DI, see above), and C-Reactive Protein (CRP).

21.4 Pharmacokinetic Assessments

The collection, processing, packing and shipping of PK, and cytokine samples are described in a separate Lab Manual for the study.

21.4.1 PK Sample Collection

Plasma PK samples for exposure-response analysis will be taken after 1, 2, 3- and 4-weeks treatment.

21.5 Cytokine Samples

Plasma samples for CXCL13, IL-1β, IL-6, IL-10, and TNF-α analysis will be taken at baseline, after 2 weeks and 4 weeks treatment.

21.6 Biobanking

The following samples are kept at frozen storage in a biobank or similar, as applicable per country, during the study:

- Cytokines (CXCL13, IL-1β, IL-6, IL-10, and TNF-α), plasma
- PK, plasma

Analysis of all cytokines and PK will be performed at a central laboratory (Eurofins ADME BIOANALYSIS, 75A Avenue de Pascalet, 30310 Vergèze, France). The samples will be sent and analyzed on a regular basis.
All samples will be destroyed immediately after analysis. No samples are kept for future research.

Instructions for collection, processing, handling, and shipment of the frozen samples will be outlined in a laboratory manual.

The total volume of blood for biobanking is approximately 46 mL.

As France is part of the EU, the Data Protection Regulation and the Data Protection Act will be respected.

21.7 Total Volume of Blood

The total volume of blood to be collected from any subject during the trial will be up to 180 mL across 7 visits and will not exceed 36 mL at any one visit (see Table 6).

Table 6: Volume of Blood during the Trial

(mL blood)	Lab. Tests[1]	PK (plasma)	Cytokine samples (plasma)	CXCL13 samples (plasma)	Maximum per Visit
Visit 1, Screening Visit	36	0	0	0	36
Visit 2, Baseline Visit	17	0	5	5	27
Visit 3, 1. week treatment	15	4	0	0	19
Visit 4, 2. week treatment	17	4	5	5	31
Visit 5, 3. week treatment	15	4	0	0	19
Visit 6, 4. week treatment	17	4	5	5	31
Visit 7, final visit	17	0	0	0	17
Total during study	134	16	15	15	**180**

1: Laboratory tests include a 15 mL blood sample for the analysis of hematology, biochemistry parameters, TSH, T4, T3, and serum β-HCG (pregnancy test at screening), as applicable, according to the study flowchart.

22 SAFETY

Adverse events will be monitored from the time that the subject gives informed consent and throughout the study, and will be elicited by direct, non-leading questioning or by spontaneous reports. Further details for AE reporting can be found in section 18.4.

Conditions that started before signing the informed consent and for which no symptoms or treatment are present until the first administration of study drug (e.g., seasonal allergy without acute complaints), are recorded as medical/surgical history.

22.1 Definitions

Adverse Events (AE): According to the International Conference of Harmonization (ICH), an AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal or investigational product, whether or not considered related to the medicinal or investigational product. Pre-existing conditions which worsen during a study are to be reported as AEs.

Adverse Reaction (AR): All untoward and unintended responses to an investigational medicinal product related to any dose administered.

Serious Adverse Events (SAE): An SAE is any AE occurring at any dose that in the view of either the investigator or sponsor, results in any of the following outcomes:

- Results in death, or
- Is life threatening, that is any event that places the patient at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death, or
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

- Hospitalization is defined as any in-patient admission (more than 24 hours).
- Prolongation of hospitalization is defined as any extension of an in-patient hospitalization beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the investigator or treating physician. Prolongation in the absence of a precipitating, treatment-emergent, clinical AE (i.e., not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting.
- Preplanned or elective treatments/surgical procedures should be noted in the subject's screening documentation. Hospitalization for a preplanned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.

Planned hospitalizations that occur exclusively for study procedures must not be documented as SAEs.

Serious Adverse Reaction (SAR): Any serious adverse experience considered by the investigator to be related to the investigational product is a SAR.

Suspected Unexpected Serious Adverse Reactions (SUSARs): SUSARs are serious reactions that are not listed in the IB and that the investigator identifies as related to the investigational product or procedure.

22.2 Severity Classification

The severity of an event is evaluated in order to subcategorize events. Severity is *not* seriousness. A very severe event can be non-serious, and a serious event can be of mild severity. All AEs (including SAEs) are to be recorded on the AE page of the subject's eCRF. Each event will be graded for severity using Common Terminology Criteria for Adverse Events (CTCAE), v4.03 grading scale: June 14, 2010.

The following grading will apply:

- Mild (Grade 1) - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate (Grade 2) - Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental Activity of Daily Living (ADL).

- Severe (Grade 3) - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Life-threatening (Grade 4) - Life-threatening consequences; urgent intervention indicated.
- Death (Grade 5) related to AE.

22.3 Relationship to Study Drug

A determination will be made of the relationship (if any) between an adverse event and the study drug. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the study drug.

The investigator should determine the relationship of an AE to the study drug after thorough consideration of all facts that are available and will be assessed using the following definitions:

- **Definitely not related**: Temporal relationship to study drug administration is missing or implausible, or there is an evident other cause
- **Probably not related**: Temporal relationship to study drug administration makes a causal relationship improbable; and other drugs, chemicals, or underlying disease provide plausible explanations
- **Possibly related**: The AE occurred in a reasonable time after study drug administration but could be related to an underlying disease, environmental or toxic factors, or other drug or therapy
- **Probably related**: Reasonable time sequence to the administration of study drug and unlikely to be attributed to concurrent disease or the drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required
- **Definitely related**: Plausible time relationship to study drug administration and event cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary

22.4 Reporting Procedures of Adverse Events

The responsible for ensuring that all AEs (as defined in Section 18.1) observed by the staff at the clinic or reported by subjects are collected and recorded in the subject's medical notes and the eCRF. The condition of each subject will be monitored throughout the study.

All AEs will be reported starting from the time informed consent for study participation is provided and until the final visit (End of Study/Early Termination visit) has occurred. All AEs that are ongoing at the subject's last visit must be followed until resolution or for 4 weeks after the study drug administration, whichever comes first.

A cluster of signs and symptoms that results from a single cause should be reported as a single AE (e.g., fever, elevated WBC, cough, abnormal check x-ray, etc. can all be reported as Pneumonia). The investigator must assign the following adverse event attributes: adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known); dates of onset and resolution; severity; assessment of relatedness to investigational product and action taken.

22.5 Reporting Procedures for Serious Adverse Events

All SAE reporting start at the time the subject has been administered the first dose of study drug and until end of study visit. Ongoing SAEs must be followed until the event resolves, or the event sequelae stabilize, or it is unlikely that any additional information can be obtained.

In the event of an SAE, the investigator must:

- Complete the provided SAE report Form with the following information, as a minimum:
    - valid EudraCT number,
    - sponsor study number,
    - one identifiable coded subject,
    - one identifiable reporter,
    - one SUSAR,
    - one suspect IMP (including active substance name- code),
    - A causality assessment.

- All SAEs are to be reported to the sponsor (or designee) within 24 hours of awareness of the event. Send it to:
    - **PharmaLex contact information**: pv-nordic@pharmalex.com
- Obtain and maintain in the subject's medical record all pertinent medical records, information, and medical judgments from colleagues, who assisted in the treatment and follow-up of the subject.
- Provide PharmaLex with additional information that may become available using the SAE reporting form. All documents submitted to PharmaLex that contains information regarding the SAE must be redacted (blacked out) for protected confidential health information, including subject initials. The assigned subject screening number should instead be recorded on each of the documents.

22.6 Reporting of SAE and SUSAR to the Competent Authorities

In the event of a fatal and life-threatening SUSAR, the sponsor should report at least a minimum of information to the CA, IECs/IRBs no later than 7 days after being made aware of the event. SUSARs which are not fatal and not life-threatening are to be reported within 15 days of awareness. When/if follow up information becomes available, this should be submitted to the authorities within 15 days of receipt.

PharmaLex should compile and submit listings of all SARs in a Development Safety Update Report (DSUR) to the CA, IECs/IRBs once a year, as applicable.

22.7 Expedited Reporting

The sponsor will ensure that processes are in place for submission of reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the study to the CA, IECs/IRBs and other investigators concerned by study drug. Reporting will be done in accordance with the applicable regulatory requirements.

22.8 Contraception and Pregnancy

The effects of AP1189 on a fetus during pregnancy are unknown. Therefore, women who are of childbearing potential should use one of the below contraceptive methods which, when used consistently and correctly are considered as highly effective birth control methods. Contraception must be used during the study and two weeks after the last IMP has been taken (equal to 5 times T1/2).

Highly effective birth control methods to be used during the study:

> Oral contraceptives, implant, transdermal patch contraceptives, injection contraceptives, intravaginal contraceptive ring, and intrauterine device (IUD) or depot injection.

Sterile or non-fertile subjects are exempt from the requirement for contraception. To be considered sterile or non-fertile, one should generally be surgically sterilized (vasectomy / bilateral tubectomy, hysterectomy and bilateral ovariectomy) or be postmenopausal, defined as missed menstruation for at least 12 months prior to enrollment in the study.

In addition, true abstinence (total abstinence from heterosexual intercourse) when this is in line with the preferred and usual lifestyle of the subject.

At all visits, subjects should be reminded of the importance of maintaining contraception and avoiding pregnancy during the study.
Subjects with a positive pregnancy result prior to baseline (Day 0) will not be eligible to participate in the study. If a female subject becomes pregnant during the treatment period of the study, she must stop taking the study medication and immediately inform the investigator. The investigator should report all pregnancies within 24 hours to PharmaLex on an SAE report Form provided. The investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until the conclusion of the pregnancy. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Male subjects: Either the partner uses one of the above safe methods or the subject and his partner use double barrier meaning condom in combination with a diaphragm. Male subjects must inform their partner(s) of the risks of becoming pregnant and for reporting any pregnancy to the study doctor.

22.8.1 Additional Reporting Requirements for Pregnancies

If a female subject of childbearing potential becomes pregnant during the study, the coordinating investigator will immediately notify the sponsor, within 24 hours of being made aware of the event. Complete the provided Pregnancy Report Form and send it to:

- PharmaLex (or designee) contact information: pv-nordic@pharmalex.com

The investigator should follow any subject who becomes pregnant, while participating in a clinical study, throughout the pregnancy. The investigator should document the outcome of the pregnancy and provide a copy of the documentation to the PharmaLex.

23 Statistical Considerations and Methods

23.1 General Considerations

Before breaking the treatment codes, all decisions on the evaluability of the data from each individual subject will be made and documented, and each subject will be assigned to the appropriate analysis data set. The following analysis sets will be used for the statistical analysis:

Safety: All subjects who received the study medication at least once, analyzed by received treatment

PK: All the subjects who completed the study and did not have any protocol deviation or events implying a bias for the PK evaluation

Efficacy: All randomized subjects who received the study medication at least once, analyzed by randomized treatment (intention to treat). A second analysis of the primary efficacy endpoint, for robustness, will be performed for all randomized subjects who complete the study without any major protocol violations (per protocol)

A Statistical Analysis Plan (SAP) describing the planned statistical analyses in detail, including interim analyses, will be prepared by CroxxMed, and validated by the sponsor prior to any unblinding of data.

23.2 Determination of Sample Size

Calculations of sample size are based on a 95% confidence interval for the mean change in CDAI from baseline.

23.2.1 Main study

For a sample size of 25 subjects, and a standard deviation for the mean change of 3 points, a 95% confidence interval will be around 2.8 points wide with 80% probability. This interval width provides a good precision of the estimate of the primary efficacy endpoint. For a sample size of 30 subjects, the interval will be around 2.5 points wide, which provides even better precision. If the sample size is larger, or if the standard deviation is smaller, the interval will be shorter (i.e., the precision will be higher). A larger standard deviation than 3 points is unlikely. SAS proc power is used for the calculations.

The study is designed to provide a minimum of 30 subjects in each of the treatment groups that proceed to Part 2, and a total of 90 patients.

23.2.2 Sub-study

For the countries in the sub-study, a smaller effect size is expected compared to the main study. Thus, a smaller variation (standard deviation) is expected for the mean change in CDAI from baseline. For a sample size of 15 subjects and a standard deviation for the mean change of 2.5 points, a 95% confidence interval will be around 3.2 points wide with 80% probability. This interval width provides an acceptable precision of the estimate of the primary efficacy endpoint.

The sub-study is designed to provide a minimum of 15 subjects in each of the treatment groups (Part 2 only).

23.3 Study Participant Characteristics

The following demographic parameters will be analyzed by descriptive statistics:

- Demographic characteristics (including age, weight, and height)

- Medical history

23.4 Safety Analysis

The primary safety endpoint is the safety of AP1189 against placebo by evaluating adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities. All safety parameters (ECG, vital signs, AEs/SAEs, laboratory abnormalities, etc.) will be summarized by treatment and time point.

23.5 Efficacy Analysis

All efficacy endpoints will be evaluated by treatment group using descriptive statistics. Confidence intervals will be presented where appropriate.

23.5.1 Analysis of Primary Efficacy Endpoints

The change in CDAI after 4 weeks of treatment compared to baseline will be evaluated by assessing the following descriptive statistics by treatment group:

- Mean change in CDAI from baseline to week 4 (with confidence interval for the mean change)
- Proportion of subjects with a change in CDAI score from severe (CDAI > 22) to moderate (CDAI ≤ 22) at week 4 compared to baseline (with Clopper-Pearson confidence interval for the proportion)

23.5.2 Analysis of Secondary Efficacy Endpoints

The effects of AP1189 against placebo will be evaluated by descriptive statistics, assessing the following by treatment group:

- Proportion of subjects achieving a reduction of more than 10 (ten) swollen and/or tender joints (SJC and TJC, summarized) at week 4 compared to baseline
- Proportion of subjects achieving a change in CDAI score after 4 weeks of treatment compared to baseline
    - Proportion of subjects with a 5-point decrease
    - Proportion of subjects with a 10-point decrease
    - Proportion of subjects with a 15-point decrease
- Proportion of subjects achieving a change in DAS28 from DAS28 > 3.2 to DAS28 ≤ 3.2 at week 4 compared to baseline
- Change of HAQ-DI at week 4 compared to baseline
- Change of FACIT-Fatigue at week 4 compared to baseline
- Proportion of subjects achieving ACR response assessed by ACR 20, ACR 50, and AC70

23.5.3 Analysis of Tertiary Efficacy Endpoints

The effect of AP1189 compared to placebo will be further evaluated by descriptive statistics, assessing the following by treatment group:

- CXCL13, IL-1β, IL-6, IL-10, and TNF-α at week 4 compared to baseline
- Synovial biopsy at baseline and after 4 weeks treatment (only Part 2 at selected sites)

23.5.4 Analysis of other Endpoints (if applicable)

The following efficacy parameters will be summarized by treatment and time point, using descriptive statistics:

- Investigator Global VAS
- Patient Pain VAS
- CRP

23.6 Pharmacokinetic Analyses

Descriptive statistics will be used for an exploratory description of exposure in relation to effect. Plasma concentrations will be used to measure exposure.

23.7 Interim Analyses

An independent external statistician will conduct the interim analysis.

All safety parameters (ECG, vital signs, AEs/SAEs, laboratory abnormalities, etc.) and efficacy data for the primary efficacy endpoint will be summarized by treatment and time point for the subjects included in Part 1 of the study. The choice of design for Part 2 will be based on the results from the interim analysis.

The independent external statistician will ensure that the interim analyses are a completely confidential process, investigators and other study personnel will be kept blind and will only be informed about the decision of design choice for Part 2 of the study.

24 Data Management and Quality Assurance

24.1 Subject Records and Source Data

24.1.1 Record Retention

To enable evaluations and/or audits from regulatory authorities or sponsor, the investigator agrees to keep records. The records must include the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed informed consent documents, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The investigator should retain the records according to ICH, local regulations, or as specified in the Clinical Study Agreement (CSA).

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the sponsor, such as another investigator, another institution, or an independent third party arranged by the sponsor. Investigator records must be kept for a minimum of 25 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain sponsor's written permission before disposing of any records, even if retention requirements have been met.

24.1.2 Source Documents

It is essential that the patient record contains all important details about the subject's participation in the study. The investigator or designated person will agree, as a minimum requirement, to record the following information in the patient record:

The following information should be entered in the subject's source documents:

- Study number, brief description, or title of the study
- The date that the subject gave written consent
- The date of all subject visits
- Medical history, including a detailed history of the study disease
- Documentation of all procedures conducted during the trial
- All concurrent medications (list all prescription, non-prescription, and herbal medicine being taken at the time of enrolment). At each subsequent visit, changes to the list of medications and concurrent procedures should be recorded
- Occurrence and status of any adverse events
- All SAEs
- The date the subject exited the study, and a notation as to whether the subject completed the study or the reason for discontinuation.

In most cases, the source documents are the hospital's or the physician's patient record. In these cases, data collected in the eCRFs must match the data in those charts.

In some cases, the eCRF, or part of the eCRF, may also serve as source documents. In these cases, it will be described in a source data location form and available at the investigator's site as well as in the Trial Master File (TMF) and clearly identify those data that will be recorded in the eCRF, and for which the eCRF will stand as the source document.

24.1.3 Electronic Case Report Form

In this study, the term eCRF is used as an abbreviation for an electronic data report form. The eCRF includes recordings of all study data from each subject. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency and completeness of the data. Queries will be issued within the system to solve discrepancies. An electronic audit trail will be used to track all data changes in the database.

24.1.3.1 Case Report Form Completion

An eCRF is required and should be completed for each included subject. The completed original eCRF are the sole property of SynAct Pharma and should not be made available in any form to third parties, except for authorized representatives of SynAct Pharma or appropriate regulatory authorities, without written permission from SynAct Pharma.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the eCRF and any other data collection forms (source documents) and ensuring that they are

accurate, authentic/original, attributable, complete, consistent, legible, timely, enduring and available when required. The eCRF must be signed by the investigator or by an authorized staff member to attest that the data contained on the eCRF is true. Any corrections to entries made in the eCRF, source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry. For eCRFs, this is handled within the data entry system.

24.1.3.2 Missing Data

If any information is not available, and the investigator considers that it will never be available (e.g., the weight on a particular visit was not recorded), the investigator will document the missing value in the eCRF and, if appropriate, explain, in a comment in the eCRF, why the investigation was missed out (e.g., the subject was not well enough to undergo the procedure). Details on the statistical analysis of missing data will be described in the Statistical Analysis Plan (SAP).

24.2 Storage and Archiving

If the investigator leaves the employment at the hospital, he/she will inform the sponsor and nominate a contact person who will have access to the study documents. The investigator should take measures to prevent accidental or premature destruction of these documents.

Essential documents shall be archived in such a way that ensures that they are readily available upon authorities' request.

The Investigator Site File (ISF) must not be destroyed without the sponsor's approval.

24.3 Monitoring and Quality Control/Assurance

This study will be monitored at all stages by the clinical research personnel designated by the sponsor; CroxxMed ApS. Monitoring will include personal visits and telephone communication to ensure that the investigation is conducted according to the protocol and complies with GCP guidelines and applicable regulatory requirements. The on-site review of eCRFs will include a review of forms for completeness, clarity, and consistency with source documents available for each subject.

Source data as defined by ICH GCP are all original documents, records, and data such as patient records, hospital records, laboratory notes, subject diaries, or imaging data.

To this end, the investigator agrees to allow regular visits (frequency depending on recruitment) by the study monitors and to ensure they have a suitable area in which to work (e.g., a desk) and adequate access to study personnel and documents.

On-site monitoring will include source document verification (SDV). SDV is the procedure whereby the data contained in the eCRFs are compared with the primary source data (e.g., patient notes, original recordings from automated instruments, X-ray films, ECG tracings, and laboratory results) contained in the patient records held at the investigational site and thereby verified as accurate.

The investigator must be aware that:

- SDV is a part of the routine monitoring process. It will be carried out by designated study personnel and will be done in such a way as to preserve subject confidentiality, considering all ethical and legislative

requirements. SDV will be carried out by direct comparison of entries made in the eCRF with appropriate source data. Direct access to source data requires that the subject gives written, documented consent to this

- Where source data are in the form of a computer print-out (e.g., medical records, ECG tracings) they will be made available by the investigator to the monitor. Each will be signed and dated by the investigator or a designated person, confirming that the print-out is a true and faithful record of the data for that subject. These printouts will be filed on-site
- 100% SDV will be performed in this study. A source data location form will be agreed with the investigator listing all documents considered to be source data along with the location

For all subjects, subject's identity (date of birth, sex, initials, and subject screening number), the record of entry into the study and signature of informed consent must be verified from source documents as a minimum.

It is essential that the subject's participation in the study is recorded in the patient record.

All trial-specific monitoring procedures, monitoring visits, frequency and extent of source data verification will be predefined in a trial specific monitoring plan.

24.4 End of Trial

The end of the trial is defined as the last visit for the last subject (LVLS).

24.5 Audit and Inspections

The study may be audited or inspected by the sponsor (or a designated CRO), CA or IEC/IRB. If such an audit or inspection occurs, the investigator must agree to allow access to the study site, required subject records and study documents. If notified of audits/inspections by bodies other than the sponsor, the investigator is to inform the sponsor of any such inspection immediately. By signing this protocol, the investigator grants permission to personnel from the sponsor, its representatives, and CA or IEC/IRB for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in the eCRF generation, where clinically appropriate. The investigator will be informed about the outcome of the audit.

Quality control procedures regarding statistical analysis will be documented in the SAP: All equipment used in the study must be calibrated according to local standards and calibration certificates available for review.

24.6 Data processing and quality Control

The designated CRO will be responsible for data processing and quality control. Data management will be carried out as described in the CRO's standard operating procedures, which includes the generation and resolution of manual electronic data queries.

All planned data management procedures will be documented in a study-specific Data Management Plan (DMP) prior to the start of the trial. All planned validation checks will be documented and described in a study-specific Data Validation Plan.

The electronic database is located at the Electronic Data Capture (EDC) system vendor. A validated electronic audit trail will track data entry and correction. All systems are validated and compliant to the Food and Drug Administration's ordinance 21 CFR part 11.

Adverse events, baseline findings, medical/surgical history will be coded using MedDRA terminology (version 18.0 or later). Medications will be encrypted using the ATC codes (Anatomical Therapeutic Chemical (ATC) Classification System). The processes used for coding will be specified in the DMP.

25 DATA CONFIDENTIALITY

25.1 Documentation of Subject's Participation

The investigator must record subject identification data for all subjects who provide informed consent on a screening log, regardless of whether they receive any study medication.

A subject identification list, allocating subject's clear names to the study identification, must be kept in the ISF and must allow for the definite identification of any subject that is enrolled and takes part in the study. Study monitors are permitted to review the list but must not make and keep copies.

The subject's consent, study participation, the study visits, relevant medical data, concomitant treatment, and the occurrence of adverse events must be documented in the subject's patient record.

25.2 Data Protection

All parties will ensure the protection of personal subject data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.
When study data is compiled for transfer to sponsor and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code (the subject identification number) consisting of a numbering system provided by CroxxMed in order to de-identify study subjects.
The study sites will maintain a confidential list of subjects who participated in the study linking their numerical code to the subject's actual identity. In the case of data transfer, the sponsor will maintain high standards of confidentiality and protection of personal subject data consistent with applicable privacy laws.
To protect the subject 's identity, the unique subject identification number will be assigned to each study subject. This unique identification number will be assigned from a list provided by CroxxMed when the subject is first entered and will be used in lieu of the subject's name when the investigator reports AEs and/or other trial-related data. Thus, this number will appear on all study-related records for a particular subject. Personal information will be treated as confidential but may be reviewed by the sponsor, coordinating investigator, the clinical and medical monitors, the IEC/IRB and CA. The data protection principles of GCP, Directive 95/46/EC and local data protection regulations will be observed.

25.2.1 Processing of personal Data

The storage of personally identifiable data, including blood tests, is subject to compliance with the General Data Protection Regulation (GDPR) and the Danish Data Protection Act.

All information collected about the participant during the trial will be treated confidentially. Information about the name and social security number will not leave the hospital. Participants are asked to sign a Power of Attorney, which allows employees designated by SynAct Pharma as well as the health authorities access to their journal information for up to 15 years after the end of the trial.

Before a subject has given consent for participation, only the journal information required for the recruitment, such as diagnosis and medical history, is disclosed.
After consent has been given, information about the participant's health condition, demography, medical history, concomitant medication, and laboratory results will be obtained directly from the patient journal.

26 REGULATORY REQUIREMENTS

The planning and conduct of this clinical study are subject to national laws. Only when all the requirements and approvals have been obtained from CA and IEC/IRB will the study begin.

26.1 Institutional Review Board/Independent Ethics Committee

The IEC/IRB reviews the ethical, scientific, and medical appropriateness of a study.

Before study initiation, the investigator must have a written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and other written information to be provided to subjects and any updates. This approval must be obtained prior to the authorization of drug shipments to the study sites and before any study-related procedures can take place. All correspondence with the IRB/IEC should be retained in the ISF.

Any serious adverse events (SAEs) that meet the reporting criteria, as dictated by local regulations, will be reported to both the responsible Ethics Committees and CA, as required by local laws.

26.1.1 Updated Documents

The investigator must submit and, where necessary, obtain approval from the CA and IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. Also, the investigator should promptly report to the CA and/or IEC/IRB following local procedures:

- Major protocol deviation potentially affecting subject safety and integrity to eliminate immediate hazards to the trial subjects
- Changes increasing the risk to subjects and/or affecting the conduct of the trial significantly
- Any adverse drug reactions that are both serious and unexpected
- New information that may affect the safety of the subjects or the conduct of the trial adversely

The only circumstance in which an amendment may be initiated prior to CA and IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the CA and IRB/IEC and sponsor in writing immediately after the implementation.

26.2 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, GCP, as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and applicable national or regional regulations/guidelines.

The study will be conducted in compliance with the protocol. The protocol, any amendments and the subject informed consent will receive IRB/IEC approval/favorable opinion prior to initiation of the study.

All subjects will have their medical condition, safety and laboratory data closely monitored throughout the study.

All potential serious breaches must be reported to sponsor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure or debarment).

The general conclusions from the first in man Phase 1 study were:

- AP1189 administered by oral route as a suspension was well tolerated up to 800 mg in single dose and up to 200 mg daily for 14 days in repeated dose
- The most frequent TEAE observed were mild to moderate intensity GI disorders mainly in the single dose part while increasing the dose, which could be explained by the amount of vehicle in the suspension increasing with the dose leading to a consistency and taste increase of the drug. These effects did not lead to any treatment discontinuation for any subject and the GI tolerability was quite good when dosing for 14 days
- Cardiovascular safety of AP1189 under the study conditions was excellent
- A total of five (5) subjects all included in cohort 3 (200 mg AP1189/placebo) had isolated increases in aminotransferases (no concomitant changes in alkalic phosphatases or bilirubin were reported). Three of the five subjects were treated with active drug and two subjects were treated with placebo. All elevated liver enzymes had returned to normal values at the EOS visit.

Consequently, AP1189 present a good safety profile allowing its administration to patients at 50 mg or 100 mg doses for 4 weeks.

26.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject, prior to clinical study participation, including informed consent for any screening procedure conducted to establish subject eligibility for the study.

The investigator is also responsible for asking the subject if he/she agrees to have his/her primary care physician informed of the subject's participation in the current clinical study. If the subject agrees to such notification, the investigator shall notify the subject's primary care physician of the subject's participation in the study.

The acquisition of informed consent and the subject's agreement or refusal of notification of his/her primary care physician should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The person conducting the informed consent discussion will always be a licensed physician but not

necessarily the principal investigator. The original signed informed consent form should be retained following institutional policy, and a copy of the signed consent form should be provided to the subject.

The detailed process of obtaining informed consent is outlined in Appendix A.

26.4 Subject Confidentiality

The investigator must ensure that the subject´s confidentiality and integrity are maintained. In the eCRFs or other documents transferred to the sponsor, the subject identification number should identify subjects only. Documents that are not transferred to sponsor, should be kept in strict confidence by the investigator.

In compliance with GCP, it is required that the investigator and the institution permit authorized representatives of the sponsor, the CA, and the IRB/IEC direct access to review the subject's original records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

26.5 Investigator Signatory Obligations

The coordinating investigators should sign the clinical study protocol and report, indicating agreement with the analyses, results, and conclusions of the report.

27 ADMINISTRATIVE AND LEGAL OBLIGATIONS

27.1 Compensation to Investigator

The trial is initiated and financially supported by SynAct Pharma. The details of compensation are specified in separate contracts between the sponsor and the investigational sites. The below table gives a more detailed overview of the different payments:

Figure 2: Investigator Payments

Visit	Week	Total payment including Euro
Screening	V1	
Baseline	V2	
Treatment Week 1	V3	
Treatment Week 2	V4	
Treatment Week 3	V5	
Treatment Week 4	V6	
Final visit/WD	V7	
Follow-up Call	V8	
Total		

The total amount is intended to cover the costs incurred by the hospital in connection with the completion of the trial. The amount will be paid into the hospital's account. The department's staff and doctors have no financial relationship with SynAct Pharma.

27.2 Publication Policy

SynAct Pharma retains exclusive ownership of all data, results, reports, findings, discoveries, and any other information collected during this trial. Therefore, SynAct Pharma reserves the right to use the data from the present trial, in order to submit them to the regulatory authorities of any country.

By signing the Investigator Agreement, the investigator agrees that the results of this trial may be used for submission to national and/or international regulatory authorities. The regulatory bodies will be notified of the investigator's name, address, qualifications, and extent of involvement.

SynAct Pharma supports the exercise of academic freedom and has no objection to publication by the principal investigator of the results of the study based on information collected or generated by the principal investigator, whether or not the results are favorable to the SynAct Pharma product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide SynAct Pharma an opportunity to review any proposed publication or other types of disclosure of the results of the study (collectively "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to SynAct Pharma at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or SynAct Pharma product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, investigator agrees that the first publication is to be a joint publication covering all study sites and that any subsequent publications by the principal investigator will reference that first publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

SynAct Pharma fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations.

In all cases, SynAct Pharma will report the study results in an objective, accurate, balanced, and complete manner regardless of the outcome of the study or the country in which the study was conducted.

27.3 Insurance Information

In accordance with the laws and regulations of the country in which the study is performed, the sponsor will ensure its liability towards patients sustaining bodily injury as a direct result of participation in the study. All relevant documentation regarding such insurance will be filed in the TMF and/or ISF, as appropriate.

27.4 Compensation to Subjects

Subjects will not receive any compensation for participating in this study, but they may be reimbursed for the costs related to transportation covered by showing train tickets or similar.

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29 APPENDICES

29.1 Appendix A: Informed Consent Procedure

This appendix lists the procedure for the verbal information meeting and obtaining of consent from the subjects.

A possible subject, who has been diagnosed with RA in the clinic, will be contacted by the investigator and approached for the study. If the subject is expressing interest in the study, the information sheet will be handed out, and the subject will be invited to a verbal information meeting.

The information must be given by the investigator or her designee (physician), who has the scientific knowledge to the disease area and a thorough knowledge of the protocol.

The possible subject will be informed that the meeting is an inquiry for participation in a scientific trial and that the person has the right to bring a companion to the information meeting.

The possible subject's right to remain "not known on health condition" will be taken into consideration.

The verbal information will be given based on the written information document, which will be provided during the information meeting.

The information will be given in plain language, without any technical or value-laden phrases.

The information will be given in such a manner, that it is adapted to the person.

The information will take place without any disturbance or interruptions.

The possible subject will have the possibility to asked questions.

The person, giving the verbal information, is responsible for ensuring, that the possible subject has understood all information provided, before entering into the study.

Consent to participate in the study is given based on the written and verbal information and should, therefore, in the case no time for consideration is required, be given in relation to the information meeting. If time for consideration is desired, a new appointment should be made.

The responsible investigator signs the consent form in continuation of the information meeting.

If new information concerning the effect, risks, side effects, complication or inconveniences in the study is revealed during the study, or if the study design is considerably changed, the subject will be informed hereof. In such cases, the subject must re-consent to continue in the study.

If the study is prematurely discontinued, the subject must be informed hereof.

The subject will be asked if he/she agrees to have his/her primary care physician informed of his/her participation in the clinical study. If the subject agrees to such notification, the investigator shall inform the subject's primary care physician of the subject's participation in the clinical study.

29.2 Revision History

29.2.1 Protocol Version 8.0 to Protocol Version 9.0

Version Date		**Version 8.0, 04SEP2020**	**Version 9.0, 14JAN2021**
Page	**Section**	**WAS**	**IS**
18, 37	Synopsis, 15.6	The study is to be conducted at sites in Europe	The study is to be conducted at sites in Europe **and Moldova**
36	15.1 Study Design	A minimum of 90 subjects are expected to complete the study. Up to 120 subjects are planned to be enrolled to account for discontinuation rate. The rationale for the number of subjects required is outlined in the section on sample size determination. The below Figure 1 shows the general study design.	A minimum of 90 subjects are expected to complete the study**, plus 45 subjects from Bulgaria and/or Moldova for a sub-study (see Section 15.2).** Up to 120 subjects are planned to be enrolled **for the main study** to account for discontinuation rate**, and up to 60 subjects for the sub-study**. The rationale for the number of subjects required is outlined in the section on sample size determination. The below Figure 1 shows the general study design.
36	15.2 Sub-study of subjects from Bulgaria/ Moldova		**As Bulgaria and Moldova did not participate in Part 1 of the study, a sub-study has been added to investigate the effect in these two countries separately. In addition to analyzing the main study and the sub-study separately, all data will be pooled to investigate the overall effect in all participating countries.**
36	15.3 Part 1	15.2 Part 1	**15.3 Part 1 (main study only)**
37	15.4.1 Number of Subjects in Part 2	A minimum of 66 subjects is expected to complete Part 2 of the study. About 88 subjects are planned to be enrolled in accounting for discontinuation rate. The rationale for the number of subjects required is outlined in the section on sample size determination.	A minimum of 66 subjects **in the main study** is expected to complete Part 2 of the study**, and 45 subjects in the sub-study.** About 88 subjects are planned to be enrolled **in the main study** in accounting for discontinuation rate**, and about 60 subjects in the sub-study.** The rationale for the number of subjects required is outlined in the section on sample size determination.
67	23.2 Determination of Sample Size		**23.2.1 Main Study**
67	23.2 Determination of Sample Size		**23.2.2 Sub-study** **For the countries in the sub-study, a smaller effect size is expected compared to the main study. Thus, a smaller variation (standard deviation) is expected for the mean change in CDAI from baseline. For a sample size of 15 subjects and a standard deviation for the mean change of 2.5 points, a 95% confidence interval will be around 3.2 points wide with 80% probability. This interval width provides an acceptable precision of the estimate of the primary efficacy endpoint.**

			The sub-study is designed to provide a minimum of 15 subjects in each of the treatment groups (Part 2 only).

Protocol Version 7.0 to Protocol Version 8.0

Version Date		**Version 7.0, 23APR2020**	**Version 8.0, 04SEP2020**
8	**5.** Glossary of Abbreviations	-	**Statens Serums Institut (SSI)**
48 Study Flow Chart	Table 3	-	**Blood sample (MC1R genotype analysis)**
49	20.1.2 Visit 2, the Baseline Visit	Blood samples (hematology, biochemistry and TSH, T3, and T4)	Blood samples (hematology, **MC1R genotype analysis**, biochemistry and TSH, T3, and T4)
56	21.1.9.2 MC1R genotype analysis	-	**The human melanocortin receptor type 1 (MC1R) is a highly polymorphic gene. It is known that some receptor variants are associated with loss of function when characterized by the receptor's ability to induce cAMP accumulation. There is evidence that the loss of function is restricted to the cAMP pathway, i.e., the ability to stimulate the ERK phosphorylation pathway, the pathway stimulated by AP1189, for most receptor variants are preserved.** **At baseline or any other visit after randomization, a blood sample will be taken once to identify the MC1R variant in randomized patients.** **The blood sample is stored at -80 ° in a research biobank until shipment and subsequent analysis at Statens Serum Institut (SSI). The genotype sequencing method is used in the blood sample analysis, meaning that only the gene variations that have to do with the melanocortin receptor are examined.** **The company Genetelligence is responsible for the interpretation of the genetic tests, and the results are only used in the above study.** **All blood samples will be destroyed after analysis, and no samples will be saved for future research.**
56	21.1.9.3 Thyroid function	Thyroxine (T4) free, Triiodothyronine (T3) total or free, and the thyroid-stimulating hormone (TSH).	Thyroxine (T4**) total or** free, Triiodothyronine (T3) total or free, and the thyroid-stimulating hormone (TSH).

29.2.2 Protocol Version 6.0 to Protocol Version 7.0

Version Date		**Version 6.0, 22JAN2020**	**Version 7.0, 23APR2020**
Page	**Section**	**WAS**	**IS**

16 Synopsis, 35	Study design, 15.2 Part 1, and 15.3 Part 2	• Group A: AP1189 dose 50 mg (~~12~~ subjects) or • Group B: placebo (~~6~~ subjects) Steering Committee (SC) meeting • Group C: AP1189 dose 100 mg (~~12~~ subjects) or • Group D: placebo (~~6~~ subjects) INTERIM ANALYSIS Part 2: All subjects will be randomized into either design 1, 2 or 3 based on data from the interim analysis. • Design 1: AP1189 dose 50 mg (~~36~~ subjects) or placebo (~~18~~ subjects) plus MTX (10-25 mg) weekly • Design 2: AP1189 dose 100 mg (~~36~~ subjects) or placebo (~~18~~ subjects) plus MTX (10-25 mg) weekly • Design 3: Continue with the same doses as in Part 1, in a 1:1:1 ratio (AP1189 50 mg (~~18~~ subjects), AP1189 100 mg (~~18~~ subjects) or placebo (~~18~~ subjects)) plus MTX (10-25 mg) weekly	• Group A: AP1189 dose 50 mg (**min.8** subjects) or • Group B: placebo (**min. 4** subjects) Steering Committee (SC) meeting • Group C: AP1189 dose 100 mg (**min. 8** subjects) or • Group D: placebo (**min. 4** subjects) INTERIM ANALYSIS Part 2: All subjects will be randomized into either design 1, 2 or 3 based on data from the interim analysis. • Design 1: AP1189 dose 50 mg (**44** subjects) or placebo (**22** subjects) plus MTX (10-25 mg) weekly • Design 2: AP1189 dose 100 mg (**44** subjects) or placebo (**22** subjects) plus MTX (10-25 mg) weekly Design 3: Continue with the same doses as in Part 1, in a 1:1:1 ratio (AP1189 50 mg (**22** subjects), AP1189 100 mg (**22** subjects) or placebo (**22** subjects)) plus MTX (10-25 mg) weekly
20 Synopsis	Sample size considerations	The sample size is calculated to provide an acceptable precision of a ~~90~~% confidence interval for the primary endpoint, the mean change in CDAI from baseline	The sample size is calculated to provide an acceptable precision of a **95**% confidence interval for the primary endpoint, the mean change in CDAI from baseline
27	10.1.2 Summary of Result from Part IV (unblinded, non-validated data as the full report of data is still pending)	10.1.2 Summary of Result from Part IV ~~(unblinded, non-validated data as the full report of data is still pending)~~	10.1.2 Summary of Result from Part IV
28	10.1.6 Safety Conclusion from Part 4, (unblinded, non-validated data as the full report of data is still pending)	10.1.6 Safety Conclusion from Part 4~~,~~ ~~(unblinded, non-validated data as the full report of data is still pending)~~	10.1.6 Safety Conclusion from Part 4
34	15.1 Study Design	A minimum of 90 subjects are expected to complete the study. Up to 120 subjects are planned to be enrolled to account for ~~up to 25 %~~ discontinuation rate.	A minimum of 90 subjects are expected to complete the study. Up to 120 subjects are planned to be enrolled to account for discontinuation rate.
35	15.2.1 Number of Subjects **in** Part 1	A minimum of ~~36~~ subjects is expected to complete Part 1 of the study. About ~~48~~ subjects are planned to be enrolled in accounting for ~~approximately 25 %~~ discontinuation rate.	A minimum of **24** subjects is expected to complete Part 1 of the study. About **32** subjects are planned to be enrolled in accounting for discontinuation rate.
36	15.3.1 Number of Subjects in Part 2	A minimum of ~~54~~ subjects is expected to complete Part 2 of the study. About ~~72~~ subjects are planned to be enrolled in accounting for ~~approximately 25 %~~ discontinuation rate.	A minimum of **66** subjects is expected to complete Part 2 of the study. About **88** subjects are planned to be enrolled in accounting for discontinuation rate.
36	15.7 Steering Committee (SC)	The SC will review blinded laboratory data from the first ~~18~~ subjects randomized into group A or B before the next ~~18~~ subjects in	The SC will review blinded laboratory data from the first **min. 12** subjects randomized into group A or B before the next **min. 12**

		Part I, group C/D can be included and randomized.	subjects in Part I, group C/D can be included and randomized.
36	15.8 Data Monitoring Committee (DMC)	The DMC will review the unblinded data from the interim analysis of the first ~~36~~ subjects from Part 1.	The DMC will review the unblinded data from the interim analysis of the first **min. 24** subjects from Part 1.
37	15.9 Criteria for Choice of Design for Part 2	**Design 1:** AP1189 dose 50 mg (~~36~~ subjects) or placebo (~~18~~ subjects) plus MTX (10-25 mg) will be applied if: **Design 2:** AP1189 dose 100 mg (~~36~~ subjects) or placebo (~~18~~ subjects) plus MTX (10-25 mg) will be applied if: **Design 3:** Continue with the same doses as in Part 1, in a 1:1:1 ratio (AP1189 50 mg (~~18~~ subjects), AP1189 100 mg (~~18~~ subjects) or placebo (~~18~~ subjects)) plus MTX (10-25 mg) will be applied if:	**Design 1:** AP1189 dose 50 mg (**min. 44** subjects) or placebo (**min. 22** subjects) plus MTX (10-25 mg) will be applied if: **Design 2:** AP1189 dose 100 mg (**min. 44** subjects) or placebo (**min. 22** subjects) plus MTX (10-25 mg) will be applied if: **Design 3:** Continue with the same doses as in Part 1, in a 1:1:1 ratio (AP1189 50 mg (**min. 22** subjects), AP1189 100 mg (**min. 22** subjects) or placebo (**min. 22** subjects)) plus MTX (10-25 mg) will be applied if:
65	23.2 Determination of Sample Size	Calculations of sample size are based on a ~~90~~% confidence interval for the mean change in CDAI from baseline. For a sample size of ~~12~~ subjects, and a standard deviation for the mean change of 3 points, a ~~90~~% confidence interval will be around ~~3.4~~ points wide with 80% probability. This interval width provides ~~an acceptable~~ precision of the estimate of the primary efficacy endpoint. For a sample size of ~~18~~ subjects, the interval will be around ~~2.8~~ points wide, which provides ~~good~~ precision. If the sample size is larger, or if the standard deviation is smaller, the interval will be shorter (i.e., the precision will be higher). A larger standard deviation than 3 points is unlikely. SAS proc power is used for the calculations. The study is designed to provide a minimum of ~~12~~ subjects in each treatment group, and a total of 90 ~~patients~~.	Calculations of sample size are based on a **95%** confidence interval for the mean change in CDAI from baseline. For a sample size of **25** subjects, and a standard deviation for the mean change of 3 points, a **95**% confidence interval will be around **2.8** points wide with 80% probability. This interval width provides **a good** precision of the estimate of the primary efficacy endpoint. For a sample size of **30** subjects, the interval will be around **2.5** points wide, which provides **even better** precision. If the sample size is larger, or if the standard deviation is smaller, the interval will be shorter (i.e., the precision will be higher). A larger standard deviation than 3 points is unlikely. SAS proc power is used for the calculations. The study is designed to provide a minimum of **30** subjects in each **of the** treatment group**s that proceed to Part 2**, and a total of 90 **subjects**.

29.2.3 Protocol Version 5.0 to Protocol Version 6.0

Version Date		**Version 5.0, 16DEC2019**	**Version 6.0, 22JAN2020**
Page	**Section**	**WAS**	**IS**
18 Synopsis, 38 (16.2)	Main criteria for inclusion (11)	11. ~~NSAIDs (up to the maximum recommended dose) are permitted if the dose has been stable for at least 6 weeks prior to baseline~~	
19 Synopsis, 39 (16.3)	Main criteria for exclusion		**EXCLUSION CRITERIA 17-20 ONLY APPLY FOR SUBJECTS IN NORWAY:** **17. Evidence of moderate and/or severe organ dysfunction** **18. Abnormal chest x-ray (as per the discretion of the investigator)** **19. Evidence of positive hepatitis serology** **20. Evidence of peptic ulcer disease**

17 Synopsis, 36	Synopsis and section 15.5	The study is to be conducted at ~~6~~ sites ~~distributed between Denmark, Sweden and Norway~~	The study is to be conducted at sites **in Europe**
56 and Table 3, page 48	21.1.9.3	Thyroxine (T4) free, triiodothyronine (T3) total, and the thyroid-stimulating hormone (TSH). Blood samples for measuring the thyroid function will be taken at all visits	Thyroxine (T4) free, triiodothyronine (T3) total **or free**, and the thyroid-stimulating hormone (TSH). Blood samples for measuring the thyroid function will be taken at all visits
36	15.7	The SC is appointed by the sponsor and comprises of the coordinating investigators and a sponsor medical responsible person. All decisions made by the SC will be documented and signed by its members as per the SC Charter (a specific charter will be developed to define roles and responsibilities). The SC will review blinded laboratory data from the first 18 subjects randomized into group A or B before the next 18 subjects in Part I, group C/D can be included and randomized. The SC will, based on the recommendations from the data monitoring committee (DMC), decide the design for Part 2. The SC will meet ad hoc.	The SC is appointed by the sponsor and comprises of the coordinating investigators **in Denmark, Sweden and Norway** and a sponsor medical responsible person. All decisions made by the SC will be documented and signed by its members as per the SC Charter (a specific charter will be developed to define roles and responsibilities). The SC will review blinded laboratory data from the first 18 subjects randomized into group A or B before the next 18 subjects in Part I, group C/D can be included and randomized. The SC will, based on the recommendations from the data monitoring committee (DMC), decide the design for Part 2. The SC will meet ad hoc.

34, 66	14.2, 23.5.2	The effects of AP1189 against placebo will be evaluated by assessing the following by treatment group:
		• Proportion of subjects achieving a ~~reduced number~~ of swollen and tender joints (SJC and TJC, ~~respectively~~) at week 4 compared to baseline
		• Proportion of subjects achieving a change in CDAI score at week 4 compared to baseline
		  o Proportion of subjects with a 5-point decrease
		  o Proportion of subjects with a 10-point decrease
		  o Proportion of subjects with a 15-point decrease
		• Proportion of subjects achieving a change in DAS28 at week 4 compared to baseline
		• Change of HAQ-DI at week 4 compared to baseline
		• Change of FACIT-Fatigue at week 4 compared to baseline
		• Proportion of subjects achieving ACR response assessed by ACR 20, ACR 50, and AC70
			The effects of AP1189 against placebo will be evaluated by assessing the following by treatment group:
			• Proportion of subjects achieving **a reduction** of **more than 10 (ten)** swollen and**/or** tender joints (SJC and TJC **summarized**) at week 4 compared to baseline
			• Proportion of subjects achieving a change in CDAI score at week 4 compared to baseline
			  o Proportion of subjects with a 5-point decrease
			  o Proportion of subjects with a 10-point decrease
			  o Proportion of subjects with a 15-point decrease
			• Proportion of subjects achieving a change in DAS28 **from DAS28>3.2 to DAS28 ≤ 3.2** at week 4 compared to baseline
			• Change of HAQ-DI at week 4 compared to baseline
			• Change of FACIT-Fatigue at week 4 compared to baseline
			• Proportion of subjects achieving ACR response assessed by ACR 20, ACR 50, and AC70

29.2.4 Protocol Version 4.0 to Protocol Version 5.0

Version Date		**Version 4.0, 31OCT2019**	**Version 5.0, 16DEC2019**
Page	**Section**	**WAS**	**IS**
17 Synopsis, 33	Study Objectives	• Proportion of subjects achieving a reduction of more than ten swollen joints at week 4 compared to baseline • ~~Proportion of subjects achieving a reduction of more than 10 tender joints at week 4 compared to baseline~~	• Proportion of subjects achieving a reduction of more than **10 (**ten**)** swollen **and/or tender** joints at week 4 compared to baseline
18 Synopsis, 38 (16.2)	Main criteria for inclusion (4)	~~Poly~~arthritis with joint swelling and tenderness of a minimum of three joints out of 68 joints tested	**Arthritis** with joint swelling and tenderness of a minimum of three joints out of 68 joints tested
36	15.8	The DMC is established by the sponsor and consists of a group of three study independent members: two independent external experts (~~a Scientific & Medical Director (chief physician~~) and a professor and specialist in hepatology and clinical pharmacology at Bispebjerg hospital), and an independent external statistician.	The DMC is established by the sponsor and consists of a group of three study independent members: two independent external experts (**a rheumatologist** and a professor and specialist in hepatology and clinical pharmacology at Bispebjerg hospital), and an independent external statistician.
34, 66 (23.5.1)	14.1 and 23.5.1	~~The change in CDAI score from severe (CDAI > 22) to moderate (CDAI ≤ 22) after 4 weeks of treatment compared to baseline, by treatment group.~~	**The change in CDAI after 4 weeks of treatment compared to baseline will be evaluated by assessing the following, by treatment group:** • **Mean change in CDAI from baseline to week 4** • **Proportion of subjects with a change in CDAI score from severe (CDAI > 22) to moderate (CDAI ≤ 22) at week 4 compared to baseline**
45	19.1.1.1	~~In case of an increase in ALT equal to 3x the upper normal level, MTX treatment must be stopped for one week. The IMP/placebo treatment continues unchanged. After one week, treatment with MTX resumes if the liver enzymes are normalized.~~ ~~If ALT increases again, the MTX tablet treatment is changed to MTX injection. For a more detailed instruction see Appendix B.~~	**It is recommended with more frequent blood test in case of elevation of liver enzymes.** **Transaminase Increase:** **A table is added with the information from section 29.2 (minor changes added), and Section 29.2 is deleted**
52	20.1.7		**Urinalysis (dipstick)**

29.2.5 Protocol Version 3.0 to Protocol Version 4.0

Version Date		**Version 3.0, 23AUG2019**	**Version 4.0, 31OCT2019**
Page	**Section**	**WAS**	**IS**
17, 36	7, 15.5	The study is to be conducted at 6 sites distributed between Denmark, Sweden and ~~the UK~~	The study is to be conducted at 6 sites distributed between Denmark, Sweden and **Norway**

29.2.6 Protocol Version 2.0 to Protocol Version 3.0

Version Date		**Version 2.0, 20MAY2019**	**Version 3.0, 23AUG2019**
Page	**Section**	**WAS**	**IS**

6	5	CL/F Apparent total clearance Cmax Maximum plasma concentration	CL/F Apparent total clearance **CLr Renal clearance** Cmax Maximum plasma concentration
15	7	INTERIM ANALYSIS Part 2: All subjects will be randomized into either design 1, 2 or 3 based on data from the interim analysis. Design 1: AP1189 dose 50 mg (36 subjects) or placebo (18 subjects) Design 2: AP1189 dose 100 mg (36 subjects) or placebo (18 subjects) Design 3: Continue with the same doses as in Part 1, in a 1:1:1 ratio (AP1189 50 mg (18 subjects), AP1189 100 mg (18 subjects) or placebo (18 subjects))	INTERIM ANALYSIS Part 2: All subjects will be randomized into either design 1, 2 or 3 based on data from the interim analysis. Design 1: AP1189 dose 50 mg (36 subjects) or placebo (18 subjects) **plus MTX (10-25 mg) weekly** Design 2: AP1189 dose 100 mg (36 subjects) or placebo (18 subjects) **plus MTX (10-25 mg) weekly** Design 3: Continue with the same doses as in Part 1, in a 1:1:1 ratio (AP1189 50 mg (18 subjects), AP1189 100 mg (18 subjects) or placebo (18 subjects)) **plus MTX (10-25 mg) weekly**
16 32	7 12.3	Secondary efficacy objectives: (bullet point 3) • Proportion of subjects achieving a change in CDAI score • Proportion of subjects achieving a change in value to ≤ 3.2 as measured by DAS28 (disease activity score 28) at week 4 compared to baseline	Secondary efficacy objectives: (bullet point 3) • Proportion of subjects achieving a change in CDAI score **at week 4 compared to baseline** o **Proportion of subjects with a 5-point decrease** o **Proportion of subjects with a 10-point decrease** o **Proportion of subjects with a 15-point decrease** • Proportion of subjects achieving a change in value to ≤ 3.2 as measured by DAS28 (disease activity score 28) at week 4 compared to baseline
17 32 32	7 12.4 12.4	Tertiary objectives: Effects of AP1189 compared to placebo at week 4 compared to baseline on inflammatory and collagen destructive biomarkers. The biomarkers include~~, but are not limited to:~~ CXCL13 IL-1β IL-6 IL-10 and TNF-α ~~A complete list of the biomarkers to be evaluated in the study is available in the study-specific Laboratory Manual.~~	Tertiary objectives: Effects of AP1189 compared to placebo at week 4 compared to baseline on inflammatory and collagen destructive biomarkers. The biomarkers include: CXCL13 IL-1β IL-6 IL-10 and TNF-α
19 37	7 16.3	(15.3 Exclusion Criteria) 9. Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus), or gastrointestinal disease	(16.3 Exclusion Criteria) 9. Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus), or gastrointestinal disease

		10. Uncontrolled disease states, such as asthma, psoriasis, or inflammatory bowel disease where flares are commonly treated with oral or parenteral corticosteroids 11. Evidence of active malignant disease (except basal cell carcinoma of the skin that has been excised and cured) 12. Pregnant women or nursing (breastfeeding) mothers 13. History of alcohol, drug, or chemical abuse within the 6 months prior to screening 14. Neuropathies or other painful conditions that might interfere with pain evaluation 15. Body weight of >150 kg	**10. Have prior renal transplant, current renal dialysis or severe renal insufficiency (determined by a derived glomerular filtration rate (GFR) using Cockcroft Gault formula of ≤ 30 ml/min/1,73m2 calculated by the local lab** **11.** Uncontrolled disease states, such as asthma, psoriasis, or inflammatory bowel disease where flares are commonly treated with oral or parenteral corticosteroids **12.** Evidence of active malignant disease (except basal cell carcinoma of the skin that has been excised and cured) **13**. Pregnant women or nursing (breastfeeding) mothers **14.** History of alcohol, drug, or chemical abuse within the 6 months prior to screening **15**. Neuropathies or other painful conditions that might interfere with pain evaluation **16**. Body weight of >150 kg
24	10.1	In the phase I study, the first dose of AP1189 in healthy volunteers was administered in single ascending dosing using a suspension for oral administration (~~AP1189~~**SynAct**CS001 Part I), in a bioequivalence study using oral suspension as well as tablets (~~AP1189~~**SynAct**CS001 Part II) and in 14 days repeated dosing. Fourteen days repeated dosing was initiated using a tablet formulation (~~AP1189~~**SynAct**CS001 Part III) and was completed (~~AP1189~~**SynAct**CS001 Part IV) using the same suspension used in Part I**.**	In the phase I study, the first dose of AP1189 in healthy volunteers was administered in single ascending dosing using a suspension for oral administration (**SynAct**CS001 Part I), in a bioequivalence study using oral suspension as well as tablets (**SynAct**CS001 Part II) and in 14 days repeated dosing. Fourteen days repeated dosing was initiated using a tablet formulation (**SynAct**CS001 Part III) and was completed (**SynAct**CS001 Part IV) using the same suspension used in Part I.
30	11.3.2	11.3.2 Benefits and Risks of Participation ~~General conclusion from the first in man Phase 1 study:~~ • ~~AP1189 administered by oral route as a suspension was well tolerated up to 800 mg in single dose and up to 200 mg daily for 14 days in repeated dose~~ • ~~The most frequent TEAE observed were mild to moderate intensity GI disorders mainly in the single dose part while increasing the dose, which could be explained by the amount of vehicle in the suspension increasing with the dose leading to a consistency and taste increase of the drug. These effects did not lead to any treatment discontinuation for any subject and the GI~~	11.3.2 Benefits and Risks of Participation The potential benefits of participation, for all subjects in this study, is close monitoring of their medical condition and safety. Those randomized to an active treatment may have a benefit of less pain in affected joints. Subjects randomized to placebo are not expected to obtain any additional benefit, beyond close monitoring of their medical condition and safety. **Based on available non-clinical data, AP1189 appears to be well tolerated at dose levels that induce exposure well above the expected therapeutic level expected to be reached with C_{Max} values around 175 ng/ml.** **The toxicology studies showed clinical signs from the gastrointestinal system (reduced appetite, vomiting, and loose stools), the central nervous system**

		~~tolerability was quite good when dosing for 14 days~~ • ~~Cardiovascular safety of AP1189 under the study conditions was excellent~~ • ~~A total of five (5) subjects all included in cohort 3 (200 mg AP1189/placebo) had isolated increases in aminotransferases (no concomitant changes in alkalic phosphatases or bilirubin were reported). Three of the five subjects were treated with active drug and two subjects were treated with placebo. All elevated liver enzymes had returned to normal values at the EOS visit.~~ The potential benefit of participation, for all subjects in this study, is close monitoring of their medical condition and safety. Those randomized to an active treatment may have a benefit of less pain in affected joints. Subjects randomized to placebo are not expected to obtain any additional benefit, beyond close monitoring of their medical condition and safety. Consequently, AP1189 present ~~a good~~ safety profile allowing its administration to patients at 50 mg or 100 mg doses for 4 weeks. This study will provide additional efficacy and safety information on the benefit-risk profile of AP1189	**(subdued behavior). The clinical signs were most pronounced following *iv* dosing and thereby expected to be associated with high peak concentrations that hardly will be possible to reach following oral dosing. Further, AP1189 at high dose levels induced increased liver weight in rats and minipigs increased kidney weight in minipigs and increased the weight of the ovaries in female rats. Also, hypertrophy/hyperplasia of the thyroid glands was found to be most prominent in the rats. Follow-up studies in minipigs have identified that the treatment-induced increases liver weight was fully reversible following recovery associated with a fully reversible induction of phase I and phase II enzymes. Consequently, the liver findings are to be considered related to increased workload due to fully reversible phase 1 and phase 2 enzyme induction. Likewise, the follicular thyroid hyperplasia in rats most likely is associated with increased hepatic turnover of thyroid hormones.** **In Phase 1 clinical trials laboratory parameters of the thyroid gland, such as thyroid-stimulating hormone, as well as liver enzymes, has been evaluated to monitor any effect in humans. No treatment-related effects were identified on thyroid hormones. Regarding liver enzymes, temporal increases up to 1.5x the upper normal value was identified following single dosing at supratherapeutic doses (600 and 800 mg) in a few individuals. Likewise, increases in ALAT was identified following repeat dosing at the 200 ng/ml dose level where 3 out of 9 subjects showed increases above the normal upper level, where one measurement at one occasion reached 3x above the normal upper level. However, 2 out of 3 placebo-treated individuals in the same cohort of subjects did also show increases above the normal upper level. All increased in liver enzymes were without concomitant changes in alkalic phosphatases, and bilirubin, and all values returned to normal at the end of the study. Nevertheless, liver values should be carefully monitored in upcoming clinical trials, and any clinically significant increases in liver enzymes should be carefully assessed and assessed relative to the subjects' pretreatment liver function and co-medication.** **Studies on the compound's ability to induce metabolic pathways in primary**

			human hepatocytes have identified AP1189 as a weak inducer of CYP1A2 (also weak compared to omeprazole). Co-medication with compounds metabolized through the CYP1A2 pathway should therefore until further be avoided. **The cardiovascular study in minipigs showed an increase in relative heart rate at the highest dose tested (80 mg/kg). Consequently, even if this study did not reveal any treatment-related effects on blood pressure and ECG parameters, particular attention has been applied to the heart in Phase 1 clinical study. Dedicated tendency analysis on continued ECG assessments was conducted after both single and multiple dosing in Phase 1. The analyses that included testing of changes in ECG following dosing with a positive control knowing to induce QT prolongation showed no treatment effects of AP1189 on ECG or heart rate. Consequently, AP1189 has shown excellent cardiovascular safety.** **Based on AUCs, the increase seems to be supra-proportional with an increase of 2.36 for AUC0-t and 2.17 for AUC0-∞ when dose increased by 2. However, in the light of the small sample size (N = 3 or N = 6) this result should be interpreted with caution.** **Around 10% of AP1189 dose was excreted unchanged in the urine in 24 h on the dose range 50 - 800 mg. Mean CLr ranged from 2.96 to 4.68 L/h. Consequently, until specific PK evaluation in patients with severe impaired kidney function has been conducted, subjects with stage 5 Chronic Kidney Disease or higher (i.e., eGFR < 30 ml/min) should be excluded in clinical studies.** **Up to now, AP1189 has shown an excellent safety profile at all doses tested under the different conditions applied either in single or repeated administration for 14 days. As the maximum tolerated dose was not reached in Phase 1 and as the exposure following repeat dosing of AP1189 given as oral suspension showed that the exposure at the highest dose tested reached up to 5x the expected therapeutic levels, it is considered appropriate and safe to continue dosing in clinical phase 2 at the 50 and 100 mg dose levels.** **The effect of food intake on the absorption of AP1189 in the current**

			suspension formulation has not been systematically evaluated. However, it has been shown that the plasma profile of the compound, whether the first meal was served 1 hour or 4 hours post-dosing in the feasting state, is very similar. Further, it has been shown that intake of a glass of apple juice immediately after dosing does not reduce the absorption. Therefore, it is up to the subject whether they would like a glass of juice immediately after dosing. Consequently, AP1189 present **an excellent** safety profile allowing its administration to patients at 50 mg or 100 mg doses for 4 weeks. This study will provide additional safety and efficacy information on the benefit-risk profile of AP1189.
32	13	~~**13** EFFICACY ENDPOINTS~~	**13 SAFETY ENDPOINTS**
32	13.1	~~13.1 Primary Efficacy Endpoints~~ ~~The change in CDAI score from severe (CDAI > 22) to moderate (CDAI ≤ 22) after 4 weeks of treatment compared to baseline, by treatment group~~	**13.1 Primary Safety Endpoint** **The safety of AP1189 against placebo by evaluating adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities.**
33	14 and 14.1	~~13~~ EFFICACY ENDPOINTS ~~13.1~~ Primary Efficacy Endpoints The change in CDAI score from severe (CDAI > 22) to moderate (CDAI ≤ 22) after 4 weeks of treatment compared to baseline, by treatment group.	**14** EFFICACY ENDPOINTS **14.1** Primary Efficacy Endpoints The change in CDAI score from severe (CDAI > 22) to moderate (CDAI ≤ 22) after 4 weeks of treatment compared to baseline, by treatment group.
33	14.2	13.2 Secondary Efficacy Endpoints The effects of AP1189 against placebo will be evaluated by assessing the following by treatment group: • Proportion of subjects achieving a reduced number of swollen and tender joints (SJC and TJC, respectively) at week 4 compared to baseline • Proportion of subjects achieving a change in CDAI • Proportion of subjects achieving a change in DAS28 at week 4 compared to baseline • Change of HAQ-DI at week 4 compared to baseline • Change of FACIT-Fatigue at week 4 compared to baseline Proportion of subjects achieving ACR response assessed by ACR 20, ACR 50, and AC70	1**4**.2 Secondary Efficacy Endpoints The effects of AP1189 against placebo will be evaluated by assessing the following by treatment group: • Proportion of subjects achieving a reduced number of swollen and tender joints (SJC and TJC, respectively) at week 4 compared to baseline • Proportion of subjects achieving a change in CDAI **score at week 4 compared to baseline** ○ **Proportion of subjects with a 5-point decrease** ○ **Proportion of subjects with a 10-point decrease** ○ **Proportion of subjects with a 15-point decrease** • Proportion of subjects achieving a change in DAS28 at week 4 compared to baseline

			• Change of HAQ-DI at week 4 compared to baseline • Change of FACIT-Fatigue at week 4 compared to baseline Proportion of subjects achieving ACR response assessed by ACR 20, ACR 50, and AC70
34	15.3	14.3 All subjects will be randomized into one design only, either design 1, 2, or 3 based on data from the interim analysis: • Design 1: AP1189 dose 50 mg (36 subjects) or placebo (18 subjects), once daily for 4 weeks (28 days) plus MTX (10-25 mg) weekly • Design 2: AP1189 dose 100 mg (36 subjects) or placebo (18 subjects), once daily for 4 weeks (28 days) plus MTX (10-25 mg) weekly • Design 3: Continue with the same doses as in Part 1, in a 1:1:1 ratio (AP1189 50 mg (18 subjects), AP1189 100 mg (18 subjects) or placebo (18 subjects)) Following a successful screening evaluation, subjects who fulfill the enrollment criteria will be randomized accordingly.	15.3 All subjects will be randomized into one design only, either design 1, 2, or 3 based on data from the interim analysis: • Design 1: AP1189 dose 50 mg (36 subjects) or placebo (18 subjects), once daily for 4 weeks (28 days) plus MTX (10-25 mg) weekly • Design 2: AP1189 dose 100 mg (36 subjects) or placebo (18 subjects), once daily for 4 weeks (28 days) plus MTX (10-25 mg) weekly • Design 3: Continue with the same doses as in Part 1, in a 1:1:1 ratio (AP1189 50 mg (18 subjects), AP1189 100 mg (18 subjects) or placebo (18 subjects)) **plus MTX (10-25 mg) weekly** Following a successful screening evaluation, subjects who fulfill the enrollment criteria will be randomized accordingly.
35	15.8	14.8 Data Monitoring Committee (DMC) The DMC is established by the sponsor and consists of a group of three study independent members: two independent external experts (a Scientific & Medical Director (chief physician) and a specialist in ~~internal medicine and former professor of pharmacotherapy~~), and an independent external statistician. A specific DMC charter will be developed to define roles and responsibilities. The DMC will review the unblinded data from the interim analysis of the first 36 subjects from Part 1. The DMC will recommend a study design for Part 2 to the SC based on these data. All recommendations will be documented and signed by the DMC members, and they will provide a summary of the safety and tolerability data obtained in Part 1 and their design recommendation for Part 2. The independent external statistician will analyze data for the interim analysis, following the procedure described in the statistical analysis plan and the protocol. The DMC will hereafter meet ad hoc as appropriate.	15.8 Data Monitoring Committee (DMC) The DMC is established by the sponsor and consists of a group of three study independent members: two independent external experts (a Scientific & Medical Director (chief physician) and a **professor and** specialist in **hepatology and clinical pharmacology at Bispebjerg hospital**, and an independent external statistician. A specific DMC charter will be developed to define roles and responsibilities. The DMC will review the unblinded data from the interim analysis of the first 36 subjects from Part 1. The DMC will recommend a study design for Part 2 to the SC based on these data. All recommendations will be documented and signed by the DMC members, and they will provide a summary of the safety and tolerability data obtained in Part 1 and their design recommendation for Part 2. The independent external statistician will analyze data for the interim analysis, following the procedure described in the statistical analysis plan and the protocol. The DMC will hereafter meet ad hoc as appropriate.

35	15.9	14.9 Criteria for Choice of design for Part 2 **Design 1:** AP1189 dose 50 mg (36 subjects) or placebo (18 subjects) will be applied if: **Design 2:** AP1189 dose 100 mg (36 subjects) or placebo (18 subjects) will be applied if: **Design 3:** Continue with the same doses as in Part 1, in a 1:1:1 ratio (AP1189 50 mg (18 subjects), AP1189 100 mg (18 subjects) or placebo (18 subjects)) will be applied if:	15.9 Criteria for Choice of design for Part 2 **Design 1:** AP1189 dose 50 mg (36 subjects) or placebo (18 subjects) **plus MTX (10-25 mg)** will be applied if: **Design 2:** AP1189 dose 100 mg (36 subjects) or placebo (18 subjects) **plus MTX (10-25 mg)** will be applied if: **Design 3:** Continue with the same doses as in Part 1, in a 1:1:1 ratio (AP1189 50 mg (18 subjects), AP1189 100 mg (18 subjects) or placebo (18 subjects)) **plus MTX (10-25 mg)** will be applied if:
36	15.10	14.10 Stopping Rules In case of occurrence of a serious medical event (e.g., stroke, convulsion, etc.) or any SAE considered as related to the study drug, the DMC could decide to ~~ask for~~ unblind~~ing to put~~ the study~~ on hold~~. After that, depending on the results of the unblinding, the study could either be stopped or continued.	15.10 Stopping Rules In case of occurrence of a serious medical event (e.g., stroke, convulsion, etc.) or any SAE considered as related to the study drug, the DMC could decide to **put the study on hold to** unblind the study. After that, depending on the results of the unblinding, the study could either be stopped or continued.
38	16.5.2	~~15.5.2~~ Discontinuation of Individual Subjects The investigator may also withdraw a subject from the treatment or the study for any of the following reasons: • If a subject who does not meet enrolment criteria is inadvertently enrolled • Enrolment in any other clinical trial with a study drug • If the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to the introduction of the new agent • ~~The investigator stops the subject's participation in the study for~~ medical or safety reasons • If a female becomes pregnant In case of early subject discontinuation and the reason for discontinuation (if it is known) will be registered in the eCRF and source documentation. The sponsor can also decide to end the study for safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP. If the sponsor decides to stop the study, the subject should be informed of the reason hereof.	**16.5.2** Discontinuation of Individual Subjects The investigator may also withdraw a subject from the treatment or the study for any of the following reasons: • If a subject who does not meet enrolment criteria is inadvertently enrolled • Enrolment in any other clinical trial with a study drug • **In case of severe worsening of symptoms, the investigator will be able to provide joint injections with corticosteroid as rescue medication. The use of local joint injection will be at the discretion of the investigator. The IMP/placebo treatment will continue as planned** • If the subject, for any reason, requires treatment with another therapeutic agent **(rescue medication not included)** that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to the introduction of the new agent • **For** medical or safety reasons • If a female becomes pregnant In case of early subject discontinuation and the reason for discontinuation (if it is known) will be registered in the eCRF and source documentation.

			The sponsor can also decide to end the study for safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP. If the sponsor decides to stop the study, the subject should be informed of the reason hereof.
39	17.1	~~16.1~~ Subject Identification Each subject who signs the informed consent will be assigned a unique subject number (01-101 site 1, 02-101 ~~site 2,~~ etc.), which will be used as the subject's identification in the eCRF and on all source documentation throughout the study. The screened subjects will be consecutively numbered, and the first number ~~at the screening list~~ will be used ~~to the first subject screened~~. In the case of re-screening, a new screening number will be allocated. Subjects who are assigned a subject number but fails the randomization will be registered as a screen failure on the screening list.	**17.1** Subject Identification Each subject who signs the informed consent will be assigned a unique subject number (01-1**0**01 site 1, 02-1**0**01 etc.), which will be used as the subject's identification in the eCRF and on all source documentation throughout the study. The screened subjects will be consecutively numbered, and the first **available** number **as listed in the CRF,** will be used. In the case of re-screening, a new screening number will be allocated. Subjects who are assigned a subject number but fails the randomization will be registered as a screen failure on the screening list **and in the CRF**.
39	17.2	~~16.2~~ Randomization and Treatment Assignment Following a successful screening evaluation, eligible subjects will be randomized into the study. Each subject will be assigned a unique randomization number in ascending order, based on a list provided by HB Medical, and assigned a protocol specified drug treatment. Randomization numbers should be assigned according to the list and should not be omitted or reused. ~~The randomization list is based on block randomization.~~ An external statistician will prepare the randomization list and emergency code envelopes. The randomization list will be kept strictly confidential, filed securely by HB Medical (or designee), and accessible only to authorized persons per HB Medical's Standard Operating Procedures (SOPs) until the time of unblinding. A copy of the list is sent to PharmaLex Denmark, who is handling the pharmacovigilance. ~~When a site has an eligible subject, they will send a Study Order Form to HB Medical. HB Medical will then prepare a batch of three treatments (for practical purposes) and send it by courier to the site together with the corresponding emergency code envelopes for the batch.~~ The study treatment will be unknown to the Clinical Research Organization (CRO) and sponsor personnel associated with the study, all subjects, the investigator, and all site personnel except for the unblinded pharmacist(s) at HB Medical and the	**17.2** Randomization and Treatment Assignment Following a successful screening evaluation, eligible subjects will be randomized into the study. Each subject will be assigned a unique randomization number in ascending order, based on a list provided by HB Medical, and assigned a protocol specified drug treatment. Randomization numbers should be assigned according to the list and should not be omitted or reused. An external statistician will prepare the randomization list and emergency code envelopes. The randomization list will be kept strictly confidential, filed securely by HB Medical (or designee), and accessible only to authorized persons per HB Medical's Standard Operating Procedures (SOPs) until the time of unblinding. A copy of the list is sent to PharmaLex Denmark, who is handling the pharmacovigilance. The study treatment will be unknown to the Clinical Research Organization (CRO) and sponsor personnel associated with the study, all subjects, the investigator, and all site personnel except for the unblinded pharmacist(s) **and personnel** at HB Medical and the unblinded statistician responsible for preparing the randomization list.

		unblinded statistician responsible for preparing the randomization list.	
41	18.3.1	~~17.3.1~~ Drug Accountability The investigator at each site must maintain adequate records documenting the receipt, use, loss, or other disposition of drug supplies. The site pharmacist/study nurse (as appropriate per country) will verify that study drug supplies are received intact and in the correct quantities which will be documented by signing and dating the Proof of Receipt. An accurate (running) inventory of study drug will be kept by the site and will include the batch number, date of receipt, subject number, date, and initials of the person who dispense the drug, and finally the date and amount of study drug each subject return to the site. A sample of the Drug Accountability Form, following instructions provided by the monitor, will also be provided to the site pharmacist/study nurse. Accountability of the study drug will be performed and verified by the monitor throughout the study duration. All unused IMP/placebo must be registered, accounted for, and returned to ~~SynAct Pharma~~ or destroyed per instructions from SynAct Pharma and according to local regulations. The investigator, subinvestigator(s), and/or site pharmacist/study nurse agree not to supply study medication to any persons not enrolled in the study.	**18.3.1** Drug Accountability The investigator at each site must maintain adequate records documenting the receipt, use, loss, or other disposition of drug supplies. The site pharmacist/study nurse (as appropriate per country) will verify that study drug supplies are received intact and in the correct quantities which will be documented by signing and dating the Proof of Receipt. **The site pharmacist/study nurse will also sign and date a Proof of Receipt for the corresponding code envelopes.** An accurate (running) inventory of study drug will be kept by the site and will include the batch number, date of receipt, subject number, date, and initials of the person who dispense the drug, and finally the date and amount of study drug each subject return to the site. A sample of the Drug Accountability Form, following instructions provided by the monitor, will also be provided to the site pharmacist/study nurse. Accountability of the study drug will be performed and verified by the monitor throughout the study duration. All unused IMP/placebo must be registered, accounted for, and returned to **HB Medical** or destroyed per instructions from SynAct Pharma and according to local regulations. The investigator, subinvestigator(s), and/or site pharmacist/study nurse agree not to supply study medication to any persons not enrolled in the study.
42	18.4	~~17.4~~ Administration and Handling of Study Drug The study drug will be dispensed four times during Part 1 and Part 2 respectively; at the Baseline Visit, visit 2, visit 3 and at visit 4. The study drug will be in a box with 8 bottles (study drug for one week's use) containing powder of either AP1189/placebo, a funnel, and a measuring cup. The subject adds 50 ml of tap water to the powder in the bottle, shakes well for about 1 minute ~~so that~~ all ~~the~~ powder ~~is~~ dissolve~~d~~ and then immediately drink the solution. ~~To ensure that the subject gets all the medicine in the bottle, the subject must rinse with 50 ml of water a few times.~~ Between each rinse, the content of the bottle is drunk. Each subject will use one bottle daily during the treatment period.	**18.4** Administration and Handling of Study Drug The study drug will be dispensed four times during **a subject's participation in** Part 1 and Part 2 respectively; at the Baseline Visit, visit 2, visit 3 and at visit 4. The study drug will be in a box with 8 bottles (study drug for one week's use) containing powder of either AP1189/placebo, a funnel, and a measuring cup. The subject adds 50 ml of tap water to the powder in the bottle, shakes well for about 1 minute **allowing** all powder **to** dissolve and then immediately drink the solution. **The subject must rinse the bottle two times with 50 ml water to ensure ingesting all the medicine in the bottle.** Between each rinse, the content of the bottle is drunk. Each subject will use

		The subjects will be instructed to take the suspension once daily in the morning during the treatment period~~, except on~~ visit days, ~~where no~~ medication should be taken ~~before~~ after blood sampling has been done. At the Baseline Visit, the subject will receive a diary to make daily records of what time the treatment is taken. The investigator or her/his designee is responsible for explaining the correct use of the study drug and the diary to each subject, and the subjects will receive a written instruction too. Subjects will be instructed to return empty bottles, unopened bottles and the diary at each visit.	one bottle daily during the treatment period. The subjects will be instructed to take the suspension once daily in the morning **about an hour before breakfast** during the treatment period. **It is up to the subject whether they would like to drink a glass of apple juice immediately after dosing. On the** visit days, **the** medication should **first** be taken after blood sampling has been done. At the Baseline Visit, the subject will receive a diary to make daily records of what time the treatment is taken. The investigator or her/his designee is responsible for explaining the correct use of the study drug and the diary to each subject, and the subjects will receive a written instruction too. Subjects will be instructed to return empty bottles, unopened bottles and the diary at each visit. **The effect of food intake on the absorption of AP1189 in the current suspension formulation has not been systematically evaluated. However, it has been shown that the plasma profile of the compound, whether the first meal was served 1 hour or 4 hours post-dosing in the fasting state, is very similar. Further, it has been shown that intake of a glass of apple juice immediately after dosing does not reduce the absorption.**
43	19.1.1	~~18.1.1~~ Methotrexate (MTX) All subjects should follow the local guideline for starting treatment with MTX and continue MTX treatment throughout their participation in the study. MTX is not provided by the sponsor, as it is part of the patients' regular treatment.	**19.1.1** Methotrexate (MTX) All subjects should follow the local guideline **for each hospital and/or country** for starting treatment with MTX and continue MTX treatment throughout their participation in the study. MTX is not provided by the sponsor, as it is **not background treatment but** part of the patients' regular treatment.
44	19.1.3	~~18.1.3~~ Oral Corticosteroids Oral corticosteroids are prohibited within 2 weeks prior to screening and during the entire treatment period and until the final visit (Visit 7).	**19.1.3** Oral Corticosteroids Oral corticosteroids are prohibited within 2 weeks prior to screening and during the entire treatment period and until the final visit (Visit 7). **Refer to section 19.2 for treatment of asthma patients.**
44	19.2	~~18.2~~ Prohibited Medicines The following medications and therapies are not permitted during the trial and would require discontinuation of trial treatment: • Oral, intramuscular, intravenous or intra-articular corticosteroids (permitted after week 5) • Biologic therapies for RA	**19.2** Prohibited Medicines The following medications and therapies are not permitted during the trial and would require discontinuation of trial treatment: • Oral, intramuscular, intravenous or intra-articular corticosteroids (permitted after week 5). **(Asthma patients on stable prophylactic treatment are allowed to use an inhalation**

		• Intravenous immunoglobulin therapy and/or plasmapheresis New therapies for RA should not be initiated during the trial. Initiation of any new immunosuppressant or immunomodulatory therapy would be considered a treatment failure and should result in withdrawal of the subject from the IMP	**spray containing adrenocortical hormone. Furthermore, Beta-2 stimulating inhalants with short-term effects (SABA) are allowed for an asthma attack to an otherwise well-controlled asthma patient in the opinion of the investigator)** • Biologic therapies for RA • Intravenous immunoglobulin therapy and/or plasmapheresis • New therapies for RA should not be initiated during the trial. Initiation of any new immunosuppressant or immunomodulatory therapy would be considered a treatment failure and should result in withdrawal of the subject from the IMP. **As a signal for CYP1A2 induction has been observed at 10 µM in a study with human hepatocyte the following CYP1A2 substrates are also prohibited:** **Alosetron** **Clozapine** **Flutamide** **Frovatriptan** **Melatonin** **Mexiletine** **Mirtazapine** **Olanzapine** **Ramelteon** **Rasagiline** **Ropinirole** **Tacrine** **Theophylline** **Tizanidine** **Triamterene** **Zolmitriptan**
45	19.4	~~18.3~~ Treatment Compliance	**19.4** Treatment Compliance
45	19.3		**19.3 Rescue Treatment** **In case of severe worsening of symptoms, the investigator will be able to provide joint injections with corticosteroid as rescue medication. The use of local joint injections will be at the discretion of the investigator. The IMP/placebo treatment will continue as planned.**
51	21.1.2	~~20.1.2~~ Prior and Concomitant Medication Prior medications/therapies will be reported if taken up to 4 weeks prior to the Screening Visit. Concomitant medications/ therapies, will be reported at every visit throughout the trial.	**21.1.2** Subject Identification Prior medications/therapies will be reported if taken up to 4 weeks prior to the Screening Visit. Concomitant medications/ therapies, **herbal medication, and over-the-counter medication** will be reported at every visit throughout the trial.
52	21.1.5	~~20.1.5~~ Height and Weight	**21.1.5** Height and Weight

		Subject height will be measured at the Screening Visit, while weight will be assessed at all visits except at the visit ~~7 Early Withdrawal Visit.~~	Subject height will be measured at the Screening Visit, while weight will be assessed at all visits except at the visit **8 (EOS/Safety follow-up call)**.
53	21.1.8	~~20.1.8~~ X-ray A chest x-ray (only at the Screening Visit) will be used to reveal active current or history of tuberculosis and atypical mycobacterial disease, clinically significant abnormalities on chest x-ray as determined by the investigator. ~~If the subject has a chest x-ray that is no older than 6 month the x-ray can be used for the evaluation~~. X-ray of hands and feet (only at the Screening Visit): radiographic changes typical of RA on posteroanterior hand and wrist x-rays.	**21.1.8** X-ray A chest x-ray (only at the Screening Visit) will be used to reveal active current or history of tuberculosis and atypical mycobacterial disease, clinically significant abnormalities on chest x-ray as determined by the investigator. X-ray of hands and feet (only at the Screening Visit): radiographic changes typical of RA on posteroanterior hand and wrist x-rays.
54	21.1.9.2	~~20.1.9.2~~ Biochemistry Sodium, potassium, chloride, calcium, glucose, creatinine, urea, albumin, unconjugated and total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and ~~CRP~~. The biochemistry blood samples will be taken at all visits. A serum β-HCG pregnancy test will be taken at screening (dipstick pregnancy test at all other visits).	**21.1.9.2** Biochemistry Sodium, potassium, chloride, calcium, glucose, creatinine, urea, albumin, unconjugated and total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and **INR**. The biochemistry blood samples will be taken at all visits. A serum β-HCG pregnancy test will be taken at screening (dipstick pregnancy test at all other visits).
54	21.1.9.4	~~20.1.9.4~~ Urinalysis A dipstick urine test for blood, protein, and glucose will be performed at the site at the Screening Visit and Visit 7. If any of the results are abnormal, a urine sample will, be sent ~~to microscopic examination~~ at the local laboratory.	**21.1.9.4** Urinalysis A dipstick urine test for blood, protein, and glucose will be performed at the site at the Screening Visit and Visit 7. If any of the results are abnormal **and clinically significant**, a urine sample will, **at the discretion of the investigator**, be sent **for urine culture** at the local laboratory.
64	23.4		**23.4 Safety Analysis** **The primary safety endpoint is the safety of AP1189 against placebo by evaluating adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities. All safety parameters (ECG, vital signs, AEs/SAEs, laboratory abnormalities, etc.) will be summarized by treatment and time point.**
64	23.5	~~22.4~~ Efficacy Analysis All efficacy endpoints will be evaluated by treatment group using descriptive statistics. Confidence intervals will be presented where appropriate.	**23.5** Efficacy Analysis All efficacy endpoints will be evaluated by treatment group using descriptive statistics. Confidence intervals will be presented where appropriate.
65	23.5.1	~~22.4.1~~ Analysis of Primary Endpoints ~~The change in CDAI after 4 weeks of treatment compared to baseline will be evaluated by descriptive statistics, by treatment group~~.	**23.5.1** Analysis of Primary **Efficacy** Endpoints **The change in CDAI score from severe (CDAI > 22) to moderate (CDAI ≤ 22) after 4 weeks of treatment compared to baseline, by treatment group.**
64	23.5.2	~~22.4.2~~ Analysis of Secondary Endpoints The effects of AP1189 against placebo will be evaluated by descriptive statistics,	**23.5.2** Analysis of Secondary **Efficacy** Endpoints

		assessing the following by treatment group: • Proportion of subjects achieving a reduced number of swollen and tender joints (SJC and TJC, respectively) at week 4 compared to baseline • ~~Proportion of subjects with a change in CDAI score from severe (CDAI > 22) to moderate (CDAI ≤ 22) after 4 weeks of treatment compared to baseline~~ • Proportion of subjects achieving a change in DAS28 at week 4 compared to baseline • Change of HAQ-DI at week 4 compared to baseline • Change of FACIT-Fatigue at week 4 compared to baseline • Proportion of subjects achieving ACR response assessed by ACR 20, ACR 50, and AC70	The effects of AP1189 against placebo will be evaluated by descriptive statistics, assessing the following by treatment group: • Proportion of subjects achieving a reduced number of swollen and tender joints (SJC and TJC, respectively) at week 4 compared to baseline • **Proportion of subjects achieving a change in CDAI score after 4 weeks of treatment compared to baseline** ○ **Proportion of subjects with a 5-point decrease** ○ **Proportion of subjects with a 10-point decrease** ○ **Proportion of subjects with a 15-point decrease** • Proportion of subjects achieving a change in DAS28 at week 4 compared to baseline • Change of HAQ-DI at week 4 compared to baseline • Change of FACIT-Fatigue at week 4 compared to baseline • Proportion of subjects achieving ACR response assessed by ACR 20, ACR 50, and AC70
65	23.5.3	~~22.4.3~~ Analysis of Tertiary Endpoints	**23.5.3** Analysis of Tertiary **Efficacy** Endpoints
64	(22.6) is now part of 23.4	~~22.6 Safety Evaluation~~ ~~All safety parameters (ECG, vital signs, AEs/SAEs, laboratory abnormalities, etc.) will be summarized by treatment and time point.~~	The old text in 22.6 Safety Evaluation is now part of 23.4 Safety Analysis
65	23.7	~~22.7~~ Interim Analysis An independent external statistician will conduct the interim analysis. All safety parameters (ECG, vital signs, AEs/SAEs, laboratory abnormalities, etc.) and efficacy data for the primary ~~study~~ endpoint will be summarized by treatment and time point for the subjects included in Part 1 of the study. The choice of design for Part 2 will be based on the results from the interim analysis. The independent external statistician will ensure that the interim analyses are a completely confidential process, investigators and other study personnel will be kept blind and will only be informed about the decision of design choice for Part 2 of the study.	**23.7** Interim Analysis An independent external statistician will conduct the interim analysis. All safety parameters (ECG, vital signs, AEs/SAEs, laboratory abnormalities, etc.) and efficacy data for the primary **efficacy** endpoint will be summarized by treatment and time point for the subjects included in Part 1 of the study. The choice of design for Part 2 will be based on the results from the interim analysis. The independent external statistician will ensure that the interim analyses are a completely confidential process, investigators and other study personnel will be kept blind and will only be informed about the decision of design choice for Part 2 of the study.
65	24.1.1	~~23.1.1~~ Record Retention If the investigator becomes unable for any reason to continue to retain study records	**24.1.1** Record Retention If the investigator becomes unable for any reason to continue to retain study records

		for the required period (e.g., retirement, relocation), the sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the sponsor, such as another investigator, another institution, or an independent third party arranged by the sponsor. Investigator records must be kept for a minimum of ~~15~~ years after completion or discontinuation of the study or for longer if required by applicable local regulations.	for the required period (e.g., retirement, relocation), the sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the sponsor, such as another investigator, another institution, or an independent third party arranged by the sponsor. Investigator records must be kept for a minimum of **25** years after completion or discontinuation of the study or for longer if required by applicable local regulations.
68	24.4	~~23.4 Audit and Inspections~~	**24.4 End of Trial** **The end of the trial is defined as the last visit for the last subject (LVLS).**
68	24.5	~~23.4~~ Audit and Inspections	**24.5** Audit and Inspections
71	26.3	~~25.3~~ Informed Consent The acquisition of informed consent and the subject's agreement or refusal of notification of his/her primary care physician should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion ~~(~~not necessarily ~~an investigator)~~. The original signed informed consent form should be retained following institutional policy, and a copy of the signed consent form should be provided to the subject.	**26.3** Informed Consent The acquisition of informed consent and the subject's agreement or refusal of notification of his/her primary care physician should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion. **The person conducting the informed consent discussion will always be a licensed physician but** not necessarily **the principal investigator**. The original signed informed consent form should be retained following institutional policy, and a copy of the signed consent form should be provided to the subject.
79	29.2	~~28.2~~ MTX Treatment Instruction in Case of Elevation in Liver Enzymes Transaminase Increase: ALT increase ~~up to 3 times the upper limit~~ is acceptable. ~~With an increase below the three (3) times upper limit, it is recommended to draw the blood samples the day before the next MTX treatment~~. In the case of increases ~~above three (3) times upper limit~~, pause ~~or dose reduction in~~ MTX is recommended with more frequent blood test.	**29.2** MTX Treatment Instruction in Case of Elevation in Liver Enzymes Transaminase Increase: • ALT increase**s** up **to <3 X ULN (bilirubin is within the normal range)** is acceptable. **IMP and MTX remains unchanged. It is recommended to draw the blood samples the day before the next MTX treatment.** • In the case of **ALT** increases **>3 - ≤5 X ULN and bilirubin is within the normal range,** pause **IMP. Upon normalization of ALT, IMP resumes** **• In case of ALT increases >5 X ULN, MTX and IMP discontinue** **• Upon normalization of ALT (and bilirubin), MTX and IMP resume** **• At bilirubin > normal range, MTX and IMP treatment discontinue** **• IMP resumes if/when ALT is <3 X ULN and bilirubin was not elevated** **• ALT and bilirubin should be followed until normalized** **It** is recommended with more frequent blood test **in case of elevation of liver enzymes**.