The BEGIN Study: 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

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The study was conducted at sites in Denmark, Norway, Sweden, Bulgaria and Moldova

Background

Peripheral melanocortin type 1 and 3 receptors (MC1r, MC3r) are expressed on a number of immune cells including neutrophils and macrophages.
Exogenous MC1r and MC3r stimulation induces a pharmacological response that mimics endogen protective pro-resolving mechanisms including:

-Inhibition of pro-inflammatory pathways via reduction of neutrophil recruitment and inhibition of release of proinflammatory cytokines
-Stimulation of pro-resolving pathways including stimulation of macrophage efferocytosisand phagocytosis –
-both of which leads to clearance of cellular debris in the inflamed tissue

AP1189 is a novel, oral, first-in-class biased MC1r and MC3r agonist[1]. Compared with traditional MCr agonists, the compound has preference for ERK-phosphorylation and does not stimulate cAMP accumulation in pharmacological relevant concentration. In vitro and in vivo studies have shown that the anti-inflammatory and pro-resolving properties of AP1189 are comparable to the effects induced by traditional MCr agonists. Compared to traditional MCr agonist AP1189 does not induce melanogenesis[1].

AP1189 is currently in clinical development for treatment of active rheumatoid arthritis, idiopathic membranous nephropathy and acute virus induced respiratory insufficiency

Here we report the results of the Phase 2a Study conducted to evaluate the safety and tolerability and treatment effects of AP 1189 in patients with active rheumatoid arthritis (RA).

Methods

Study design and patients: The BEGIN study (SynAct- CS002) was a multicenter, two-part, randomized, double-blind, placebo-controlled 4-week study in newly diagnosed patients with active RA as determined by a Clinical Disease Activity Index [CDAI]>22 ; high disease activity (HAD) who were going to be treated with methotrexate (MTX). Part 1 of the study consisted of two cohorts of patients. Cohort 1 tested AP1189 50 mg once vs placebo. 2:1 randomization (n=14). Cohort 2 tested 100 mg vs placebo. 2:1 randomization (n=15). Following a safety review by an independent data monitoring committee the study was continued in part B where additional 76 patients were randomized to either 50 mg AP1189, 100 mg AP1189 or placebo in 1:1:1 randomization.
The total number of randomized patients were 105. – Placebo: n=34; AP1189 50 mg: n=35; AP1189 100 mg: n=36.
Efficacy evaluation was per protocol conducted on all patients who completed the study period and who did no receive any glucocorticoid treatment during the treatment period. Placebo: n=30; AP1189 50 mg n=29) and AP1189 100 mg n=34.
In all patients, study medicine were given in combination with MTX treatment with the first dose given at the same day as MTX treatment were initiated. Study medicine was given as an oral suspension once daily for 4 weeks. MTX was given in range of 10–25 mg once weekly at the investigator's discretion.

Assessments and statistical analysis: Adverse events and laboratory variables were monitored throughout the study; the primary efficacy endpoints were change from baseline in CDAI score after 4 weeks and the proportion of patients with a change in CDAI score from HDA (>22) to moderate or lower disease activity (CDAI ≤22). Descriptive statistics were used for the analysis of these result. Statistical analyses were conducted on efficacy readouts, when indicated with *; p<0.05 vs placebo.

Results

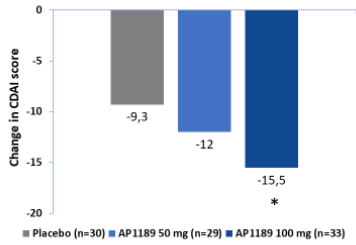
Safety evaluation:

	Placebo (n=34)	AP1189 50 mg (n=35)	AP1189 100 mg (n=36)	Total (n=105)
SAEs, n (%)	0	0	0	0
AEs, n total numbers	34	65	53	152
AE severity (mild/moderate/severe)	28/4/2	45/20/0	43/10/0	116/34/2
Discontinuation due to IMP related AEs, n	0	0	0	0
Discontinuation due to MTX related AEs, n	1	0	0	1
Most common AEs				
Nausea	7	5	8	20
Constipation/Obstipation	0	4	4	8
Headache	0	2	4	6
Increases in amino transferases	8 in 5 subjects	12 in 6 subjects- 7 of those following completion of dosing	0	20

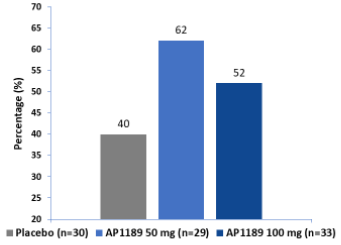
Results

Primary efficacy readout:

Mean reduction in CDAI per treatment group during the 4 weeks treatment period



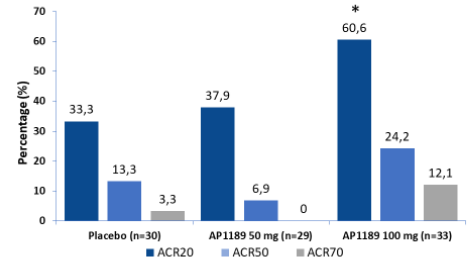
Proportion of patients with CDAI ≤ 22 by end of the 4 weeks treatment period



Results

Secondary efficacy readout:

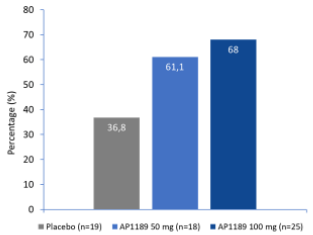
Proportion of patients achieving ACR20/50/70 response following 4 weeks treatment with AP1189 or placebo in combination with MTX



Results

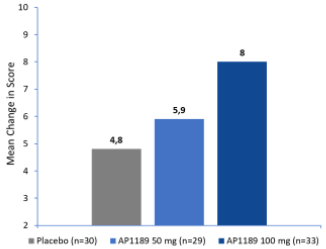
Exploratory efficacy readout:

Response rate in subset of patients with high disease activity based on DAS-28(CRP) defined as reduction to at least moderate disease activity
(>5.1 to <5.1 following 4 weeks treatment)



Secondary efficacy readout:

Mean change in FACIT-Fatigue score following 4 weeks treatment



Results

Baseline Characteristics – Subjects included in the efficacy evaluation

	Placebo (n=30)*	AP1189 50 mg (n=29)*	AP1189 100 mg (n=33)*
CDAI	36.7±8.7	36.1±9.7	39.5±9.1
SJC	10.4±379	10.2±3.9	12.1±4.9
TJC	13.7±6.1	13.6±6.0	15.2±6.0
DAS-28	5.5±1.0	5.4±0.8	5.7±0.9
Patient Global Assessment (VAS)	6.5±1.8	6.1±2.1	5.8±2.2
Physician Global Assessment (VAS)	6.2±1.1	6.3±1.3	6.4±1.3
CRP (mg/L)	18.7±26.6	14.9±18.9	26.3±41.9

All values are mean±SD. * mean baseline levels per group in the efficacy analyse set:. 2 randomised pts in each group did not complete dosing. 7 patients were per protocol taken out of the efficacy evaluation as they received glucocorticoid treatment during the treatment period. Placebo: n=2; AP1189 50 mg: n=4; AP1189 100 mg: n=1- CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS-28, Disease Activity Score in 28 joints; SJC, Swollen Joint Count; TJC, Tender Joint Count; VAS, visual analogue scale

Disclosures and acknowledgements

T. Jonassen: has ownership interest in and is an officer or board member of SynAct Pharma; **B. Telmer:** is a consultant and an independent contractor for SynAct Pharma; **I. Sandholdt:** is a consultant and an independent contractor for SynAct Pharma; **E. Hauge**: is coordinating investigator on the study. SynAct Pharma has reimbursed the hours spend to setup and coordinate the study. The study is funded by SynAct Pharma.

Summary

Safety : AP1189 was safe and well tolerated with no SAEs, no discontinuations deemed due to study drug, no infections and no discernible impact on WBC count or vital signs – No signs of immunosuppression

Efficacy:

- Significantly better CDAI improvement Vs placebo – with an established minimally important clinical difference (MCID) of 15.5-point reduction in CDAI at the 100 mg dose level compared with 9 point in the placebo group.
- Significantly higher ACR20 response than placebo (61% for 100 mg and 33% for placebo)
- Good DAS28(CRP) response in severely active patients (68% for 100 mg and 37% for placebo)
- Mean improvement in FACIT-Fatigue score that was 2x MCID (8 for 100 mg and 4.8 for placebo)
- The 50mg AP1189 dose was found to be partially effective during the 4 weeks treatment period

Perspective

The data suggest that AP1189 could be used as first line treatment in combination with MTX in moderate to severe RA. To further evaluate the compound in this patient population the EXPAND CS-007 study with 12 weeks dosing in previous treatment naïve patients has been initiated at clinical sites in Europe – for details regarding study design see: A Safety & Efficacy Study of Treatment With AP1189 in Rheumatoid Arthritis Patients naïve to DMARD Treatment - Full Text View - ClinicalTrials.gov. **In this study a newly developed immediate release tablet developed for once daily dosing is used.**
To evaluate the effect of AP1189 in DMARD –IR patients, ie patients where disease control has not been reached following a minimum of 3 months treatment with MTX, the RESOLVE studies has been setup. Recruitment to this study is planned to be initiated late in 2022. The study will be conducted at sites in US and Europe.

References

1. Montero- Melendez et al J Immunol 2015, 194:3381-8