AP1189: a novel, oral, biased melanocortin agonist with anti-inflammatory and pro-resolving effect for the treatment of rheumatoid arthritis

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Background

- Peripheral melanocortin receptors (MCr) type 1 (MC1r) and type 3 (MC3r) are expressed on a number of immune cells including, but not restricted to, neutrophils and macrophages.
- Exogenous MC1r and MC3r stimulation induces a pharmacological response that mimics the body's own protective anti-inflammatory mechanisms including:
  - inhibition of proinflammatory pathways via reduction of neutrophil recruitment and inhibition of release of proinflammatory cytokines
  - stimulation of pro-resolving pathways including stimulation of macrophage efferocytosis and phagocytosis, both of which lead to clearance of cellular debris in hyper-inflamed tissue.
- AP1189 is a novel, oral, first-in-class biased MC1r and MC3r agonist.[1] Compared with traditional MCr agonists, AP1189 is a potent inducer of erythroblast transformation specific-related gene phosphorylation (pERK), but a weak inducer of cyclic adenosine monophosphate stimulation. *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.
- AP1189 is currently in clinical development for the treatment of active rheumatoid arthritis (RA), idiopathic membranous nephropathy, and acute respiratory distress syndrome in COVID-19.
- Here we report the results of a Phase 1 study undertaken in healthy volunteers to investigate pharmacokinetic parameters of AP1189, and Part 1 results from a Phase 2 study conducted to evaluate the safety, tolerability and potential treatment effects of AP1189 in patients with RA.

Methods

Study design and patients

- The Phase 1 study was a randomized, double-blind, placebo-controlled, repeat-dosing study of oral AP1189 (50 mg [n=9], 100 mg [n=9] or 200 mg [n=9]) or placebo (n=9) given once daily for 14 days in healthy male volunteers. AP1189 or placebo as a suspension was given once daily in the fasting state. Blood samples were taken daily for safety analyses and exposure, with repeated samples for pharmacokinetic parameters taken on days 1, 7 and 14 of dosing.
- The Phase 2 study was a multicenter, two-part, randomized, double-blind, placebo-controlled 2×4-week study in newly diagnosed patients with active RA (as determined by a Clinical Disease Activity Index [CDAI] score of >22; high disease activity [HDA]) who were going to be treated with methotrexate (MTX). Patients were randomized in a 2:2:1:1 ratio to once-daily AP1189 50 mg or 100 mg (given orally as a powder dissolved in water) or placebo (two groups), plus initiation of MTX 10–25 mg weekly at the investigator's discretion for 4 weeks; this was followed by an interim analysis, then re-randomization (1:1:1) to once-daily AP1189 50 mg or 100 mg or placebo, plus MTX 10–25 mg weekly for an additional 4 weeks. This poster presents a Part 1 analysis of the first 26 patients enrolled. A minimum of 105 patients will be enrolled by study end.

Assessments and statistical analysis

- Phase 1 study: adverse events (AEs), laboratory variables and vital signs were monitored throughout the study. Standard pharmacokinetic parameters were calculated at days 1, 7 and 14 of dosing and QTc evaluation following telemetric sampling was conducted at baseline and day 14.
- Phase 2 study: AEs 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 disease activity (MDA) or low disease activity (LDA)(≤22). Descriptive statistics were used for the preliminary analysis of these results.

Results

Phase 1 study results

- AP1189 was rapidly absorbed with a median time to maximum plasma concentration observed between 1.5 h and 2.5 h, regardless of the dose and day of treatment (**Figure 1**).
- Following multiple doses, the half-life was between 19 h and 23 h with low to moderate inter-individual variability at day 14 (**Table 1**).

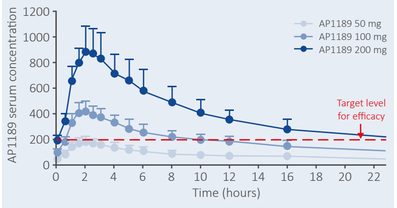
Table 1. Pharmacokinetic parameters of AP1189 following a single dose (day 1) or repeated dosing (day 14).

	Dose, mg		t_{max}, h	C_{max}, ng/mL	AUC_{0-t}, h*ng/mL	$t_{1/2}$, h
Day 1 (single dose)	50	N	9	9	9	8
		Mean	2.0	121.5	1198.9	15.7
		CV%	1.5–2.5	27.1	22.9	16.4
		GM	-	118.0	1172.8	15.5
	100	N	9	9	9	9
		Mean	1.5	297.2	2662.1	14.9
		CV%	1.5–2.5	18.1	18.7	13.6
		GM	-	292.1	2617.3	14.8
	200	N	9	9	9	9
		Mean	2.0	664.5	6050.2	13.2
		CV%	1.5–3.0	20.3	20.5	14.9
		GM	-	653.3	5949.0	13.1

	Dose, mg		t_{max}, h	C_{max}, ng/mL	AUC_{0-t}, h*ng/mL	$AUC_{0-\infty}$, h*ng/mL	k_e, 1/h	$t_{1/2}$, h
Day 14 (steady state)	50	N	9	9	9	9	9	9
		Mean	2.0	177.5	1969.9	2738.2	0.04	19.0
		CV%	1.0–2.5	20.8	23.9	31.6	23.8	21.0
		GM	-	174.4	1925.6	2633.6	0.04	18.6
	100	N	9	9	9	9	9	9
		Mean	2.0	427.1	4859.5	7521.9	0.03	20.9
		CV%	1.0–3.0	17.8	21.2	28.0	14.6	13.4
		GM	-	420.6	4767.5	7291.5	0.03	20.7
	200	N	9	9	9	9	9	9
		Mean	2.5	915.6	10067.8	15779.4	0.03	23.1
		CV%	2.0–4.0	22.0	22.3	25.0	16.5	15.6
		GM	-	897.2	9874.1	15397.7	0.03	22.8

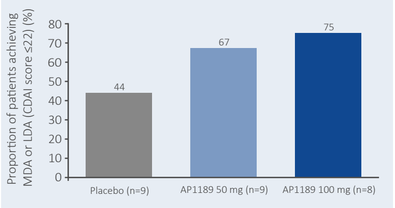
AUC_{0-t}, area under the plasma concentration–time curve; $AUC_{0-\infty}$, area under the plasma concentration–time curve during the dosing interval; C_{max}, maximum concentration; CV%, percentage coefficient of variation; GM, geometric mean; k_e, elimination rate constant; t_{max}, time to C_{max}; $t_{1/2}$, half-life.

Figure 1. Phase 1 study: The pharmacokinetic profile of AP1189 at day 14 (steady state) indicates potential for once-daily dosing.



Plasma concentration in ng/mL determined by liquid chromatography with tandem mass spectrometry from repeated blood sampling on day 14 of dosing. n=9 for each dose; values are mean and standard deviation.

Figure 2. Phase 2 study, Part 1: Patients achieving MDA or LDA (CDAI score ≤22) at the end of treatment.



CDAI, Clinical Disease Activity Index; LDA, low disease activity; MDA, moderate disease activity.

- The inter-individual variability was low to moderate for maximum plasma concentration (C_{max}) and for area under the plasma concentration–time curve (AUC_{0-t}) (<32%).
- AP1189 exposure increased with dose. C_{max} dose proportionality could not be determined; increases in AUC seemed supra-proportional with a moderate increase of 2.25 for AUC_{0-t} and 2.26 for area under the plasma concentration–time curve during the dosing interval ($AUC_{0-\tau}$) when the dose doubled.
- Mean steady-state AP1189 concentrations were reached by day 6–7.
- Accumulation of AP1189 C_{max} and AUC was observed between days 1 and 7 (geometric mean ratios between 1.4 and 1.7). No further accumulation was observed after day 7 (geometric mean ratios of ~1).
- On day 1, ~10% of the AP1189 dose was excreted unchanged in the urine in 24 h, irrespective of the dose.
- On days 1 and 14, the mean clearance was ~4 L/h, with a moderate inter-individual variability (19.2–51.4% coefficient of variance).
- A total of 38 treatment-emergent AEs (TEAEs) were reported by 17 subjects. All TEAEs were of mild (29) or moderate (9) intensity. No severe AEs or serious AEs were reported during the study.
- Only one TEAE (dyspepsia) was considered related to the study treatment, following administration of AP1189 100 mg.
- The most frequent TEAEs were nervous system disorders (13 cases of headache reported by 8 subjects) and gastrointestinal disorders (14 cases reported by 6 subjects) consisting of diarrhea (5 cases), nausea (4 cases), abdominal pain (2 cases), dyspepsia (1 case), soft feces (1 case) and vomiting (1 case).
- All subjects were dosed throughout the treatment period with no discontinuations with any dose.
- Some changes in means and individual abnormalities were observed in laboratory parameters, vital signs and electrocardiograph parameters. These changes and abnormalities were limited and were considered clinically non-significant.
- A decrease in mean total, conjugated and unconjugated bilirubin levels was observed between days 4 and 15 with AP1189 doses 100 mg and 200 mg.
- A total of five subjects (3 treated with AP1189 200 mg and 2 with placebo) had isolated increases (defined as increases above the upper limit of normal) in levels of aminotransferases (no concomitant changes in alkaline phosphatases or bilirubin levels were reported). The increases were most pronounced in the subjects treated with AP1189 200 mg, where the increase reached up to 3.6× and 2.8× the upper limit of normal.

Phase 2 Part 1 study results

- 26 patients were included in this preliminary analysis (16 females/10 males), with a median age of 57 years (range 27–77 years) and median baseline CDAI score of 34 (range 23–49).
- The median CDAI score at the end of treatment across groups was 18.5 (range 4–46); 7 patients had LDA (CDAI score 2.9–10); 9 had MDA (CDAI score 10.1–22) and 10 had HDA (CDAI score >22).
- A greater percentage of patients achieved MDA or LDA with AP1189 at treatment end compared with placebo (**Figure 2**).
- No patients discontinued the study, and no serious AEs were observed.
- The overall frequencies of AEs were comparable across the AP1189 dose groups, and slightly higher in those groups compared with placebo.
- The most commonly reported AEs were nausea (9 cases distributed equally across the three treatment groups) and headache (3 cases).
- Laboratory assessments showed no signs of immunosuppression.
- Recruitment to this study has completed and results from the full dataset will be presented by the end of 2021.

Next steps for AP1189

- Additional pharmacokinetic data for a tablet formulation will be available in quarter 4 of 2021.
- AP1189 is also being investigated in COVID-related acute respiratory distress syndrome: top-line results from a Phase 2 study reported earlier this year demonstrated a 4-day earlier respiratory recovery and a 3-day earlier hospital discharge, both versus placebo.
- Finalization of Phase 2 Part 2 is expected soon and top-line results are anticipated to be released by end of November 2021.

Conclusions

- AP1189 is a first-in-class novel, orally available compound with an anti-inflammatory effect and good tolerability profile and pharmacokinetic properties allowing for once-daily dosing, with the potential to treat active RA and other serious diseases associated with hyper-inflammation.

References

1. Montero-Melendez T et al. *J Immunol* 2015;194:3381–8.

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T. Jonassen: has ownership interest in and is an officer or board member of SynAct Pharma AB; **T. Duvauchelle:** is a consultant for SynAct Pharma AB; **B. Telmer:** is a consultant and independent contractor for SynAct Pharma AB; **I. Sandholdt:** is a consultant and independent contractor for SynAct Pharma AB; **T. Boesen:** has ownership interest in and is an officer or board member of SynAct Pharma AB; **E. Hauge:** has received honoraria as a speaker for AbbVie, Sanofi, Sobi and SynAct Pharma AB, and has received grants/research support from Novo Nordisk Foundation, Novartis and Roche.

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