Clinical trial results:
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

Summary

EudraCT number	2019-001185-15
Trial protocol	DK SE NO BG
Global end of trial date	16 November 2021

Results information

Result version number	v1 (current)
This version publication date	03 February 2023
First version publication date	03 February 2023

Trial information

Trial identification

Sponsor protocol code	SynAct-CS002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04004429
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	SynAct Pharma ApS
Sponsor organisation address	Dronninggårds allé 136, Holte, Denmark, 2840
Public contact	CSO, SynAct Pharma ApS, 45 4015 6669, tj@synactpharma.com
Scientific contact	CSO, SynAct Pharma ApS, 45 4015 6669, tj@synactpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2021
Global end of trial reached?	Yes
Global end of trial date	16 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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.

Protection of trial subjects:

Based on available non-clinical data, AP1189 appears to be well tolerated at dose levels that induce exposure well above the expected therapeutic level for this trial. Furthermore, AP1189 presents an excellent safety profile allowing administration of 50 mg and 100 mg doses for 4 weeks.

An interim analysis was performed, evaluation the first 29 patients in order to access the safety and efficacy, before proceeding. The outcome of the interim analysis was that it was safe to continue with the same doses.

The study was approved by both EC and CA prior to any screening activities. Furthermore, the Danish Medicines Agency (DMA) was consulted on the study design.

Occurrence of AE was monitored throughout the study at all visits. During and following a patient's participation in the trial, the investigator was ensuring adequate medical care to patients for any adverse events, including clinically significant laboratory values, related to the trial.

Background therapy:

The treatment with AP1189 was an add on to patients starting up on Methotrexate treatment for Rheumatoid Arthritis.

Evidence for comparator: -

Actual start date of recruitment	26 August 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Bulgaria: 31
Country: Number of subjects enrolled	Denmark: 43
Country: Number of subjects enrolled	Moldova, Republic of: 21
Worldwide total number of subjects	105
EEA total number of subjects	84

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	76
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study population consisted of newly diagnosed patients with severe active RA with a CDAI > 22 and who were to start up-titration with MTX.
Newly diagnosed patients were admitted to the hospital/clinic and evaluated for the study. If a patient was potential eligible, the patient was asked if he/she was interested to participate in the study.

Pre-assignment

Screening details:

Each potential patient signed and dated an informed consent document before any study-specified procedures were performed. Then the screening visit was performed to evaluate to the inclusion and exclusion criteria for the trial.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

All IMPs were supplied in identical appearing boxes containing bottles with screw caps, where each bottle represented one daily dosis. Each patient package contained 4 inner boxes with 8 bottles each, added up to 32 bottles per patient for a total treatment of 4 weeks,
Each bottle, inner box and outer box were carrying an investigational label, indicating that the content was intended for investigational use only. The labeling was complying with local regulatory requirement.

Arms

Are arms mutually exclusive?	Yes
Arm title	AP1189, 50 mg

Arm description:

AP1189, 50 mg, once daily for 4 weeks (28 days) plus MTX (10 25 mg) weekly

Arm type	Experimental
Investigational medicinal product name	AP1189, 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

The subject had to add 50 ml of tap water to the powder in the bottle, shake well for about 1 minute, allow all powder to dissolve, and immediately drink the solution and rinse the bottle twice with 50 ml water to ensure ingesting all the content in the bottle. Between each rinse, the content of the bottle was drunk.

Arm title	AP1189, 100 mg

Arm description:

AP1189, 100 mg, once daily for 4 weeks (28 days) plus MTX (10 25 mg) weekly

Arm type	Experimental
Investigational medicinal product name	AP1189, 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

The subject had to add 50 ml of tap water to the powder in the bottle, shake well for about 1 minute,

allow all powder to dissolve, and immediately drink the solution and rinse the bottle twice with 50 ml water to ensure ingesting all the content in the bottle. Between each rinse, the content of the bottle was drunk.

Arm title	Placebo
Arm description:	
Placebo, once daily for 4 weeks (28 days) plus MTX (10 25 mg) weekly	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

The subject had to add 50 ml of tap water to the powder in the bottle, shake well for about 1 minute, allow all powder to dissolve, and immediately drink the solution and rinse the bottle twice with 50 ml water to ensure ingesting all the content in the bottle. Between each rinse, the content of the bottle was drunk.

Number of subjects in period 1	AP1189, 50 mg	AP1189, 100 mg	Placebo
Started	35	36	34
Completed	33	34	32
Not completed	2	2	2
Consent withdrawn by subject	1	1	1
Physician decision	-	1	1
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	AP1189, 50 mg
Reporting group description:	
AP1189, 50 mg, once daily for 4 weeks (28 days) plus MTX (10 25 mg) weekly	
Reporting group title	AP1189, 100 mg
Reporting group description:	
AP1189, 100 mg, once daily for 4 weeks (28 days) plus MTX (10 25 mg) weekly	
Reporting group title	Placebo
Reporting group description:	
Placebo, once daily for 4 weeks (28 days) plus MTX (10 25 mg) weekly	

Reporting group values	AP1189, 50 mg	AP1189, 100 mg	Placebo
Number of subjects	35	36	34
Age categorical Units: Subjects			
Adults (18-64 years)	25	26	25
From 65-84 years	10	10	9
Gender categorical Units: Subjects			
Female	27	28	27
Male	8	8	7

Reporting group values	Total		
Number of subjects	105		
Age categorical Units: Subjects			
Adults (18-64 years)	76		
From 65-84 years	29		
Gender categorical Units: Subjects			
Female	82		
Male	23		

End points

End points reporting groups

Reporting group title	AP1189, 50 mg
Reporting group description:	
AP1189, 50 mg, once daily for 4 weeks (28 days) plus MTX (10 25 mg) weekly	
Reporting group title	AP1189, 100 mg
Reporting group description:	
AP1189, 100 mg, once daily for 4 weeks (28 days) plus MTX (10 25 mg) weekly	
Reporting group title	Placebo
Reporting group description:	
Placebo, once daily for 4 weeks (28 days) plus MTX (10 25 mg) weekly	

Primary: Change in CDAI

End point title	Change in CDAI
End point description:	

End point type	Primary
End point timeframe:	
The change in CDAI from severe (CDAI > 22) to moderate (CDAI <= 22) after 4 weeks treatment compared to baseline.	

End point values	AP1189, 50 mg	AP1189, 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	33	30	
Units: Number of participants	18	17	12	

Statistical analyses

Statistical analysis title	Change in CDAI
Comparison groups	AP1189, 100 mg v AP1189, 50 mg v Placebo
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.039 [2]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-6.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.05
upper limit	-0.31

Notes:

[1] - Superiority of interest but evaluated with descriptive statistics.

[2] - Post-hoc analysis

Secondary: ACR (American College of Rheumatology) Response

End point title	ACR (American College of Rheumatology) Response

End point description:

End point type	Secondary

End point timeframe:

Proportion of subjects achieving a response assessed by ACR20 after 4 weeks treatment compared to baseline.

End point values	AP1189, 50 mg	AP1189, 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	33	30	
Units: Count of Participants	11	20	10	

Statistical analyses

No statistical analyses for this end point

Secondary: ACR (American College of Rheumatology) Response

End point title	ACR (American College of Rheumatology) Response

End point description:

End point type	Secondary

End point timeframe:

Proportion of subjects achieving a response assessed by ACR50 after 4 weeks treatment compared to baseline.

End point values	AP1189, 50 mg	AP1189, 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	33	30	
Units: Count of Participants	2	8	4	

Statistical analyses

No statistical analyses for this end point

Secondary: ACR (American College of Rheumatology) Response

End point title	ACR (American College of Rheumatology) Response

End point description:

End point type	Secondary

End point timeframe:

Proportion of subjects achieving a response assessed by ACR70 after 4 weeks treatment compared to baseline.

End point values	AP1189, 50 mg	AP1189, 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	33	30	
Units: Count of Participants	0	4	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected starting from the time of signed informed consent and until the final visit (End of Study/Early Termination Visit) had occurred. Any AE that was ongoing at the final visit was followed until resolution or until four weeks after the

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	AP1189, 50 mg
Reporting group description: -	
Reporting group title	AP1189, 100 mg
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	AP1189, 50 mg	AP1189, 100 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	0 / 34 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	AP1189, 50 mg	AP1189, 100 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 35 (40.00%)	20 / 36 (55.56%)	12 / 34 (35.29%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 35 (17.14%)	0 / 36 (0.00%)	2 / 34 (5.88%)
occurrences (all)	6	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 35 (5.71%)	0 / 36 (0.00%)	1 / 34 (2.94%)
occurrences (all)	2	0	1
Diarrhoea			

subjects affected / exposed	1 / 35 (2.86%)	2 / 36 (5.56%)	0 / 34 (0.00%)
occurrences (all)	1	2	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 35 (5.71%)	0 / 36 (0.00%)	2 / 34 (5.88%)
occurrences (all)	2	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 35 (5.71%)	5 / 36 (13.89%)	0 / 34 (0.00%)
occurrences (all)	2	5	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 35 (5.71%)	1 / 36 (2.78%)	1 / 34 (2.94%)
occurrences (all)	2	1	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 35 (5.71%)	2 / 36 (5.56%)	1 / 34 (2.94%)
occurrences (all)	2	2	1
Nausea			
subjects affected / exposed	5 / 35 (14.29%)	7 / 36 (19.44%)	7 / 34 (20.59%)
occurrences (all)	5	8	7
Obstipation			
subjects affected / exposed	2 / 35 (5.71%)	1 / 36 (2.78%)	0 / 34 (0.00%)
occurrences (all)	2	1	0
Musculoskeletal and connective tissue disorders			
Arthritis rheumatoid aggravated			
subjects affected / exposed	3 / 35 (8.57%)	2 / 36 (5.56%)	1 / 34 (2.94%)
occurrences (all)	4	4	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2019	Submission to the Medical Products Agency (MPA) in Sweden. MPA's objections were addressed, and relevant changes and updates were incorporated into version 3.0 of the protocol, version 6.0 of the IB and version 6.0, Volume 2, Nonclinical and Clinical data of the IMPD (the IMPD_AP1189, Volume 1 - Pharmaceutical dossier, V5.0 dated 17MAR2019 is unchanged).
28 January 2020	Application to the Norwegian Medicines Agency (NOMA) on 5. November 2019 (protocol version 4.0 where the only addition, compared to version 3.0, was "Norway". Protocol versions 5 and 6 addressed NMA's objections and recommendations.
30 April 2020	Amendment 3 concerned a permission to continue dosing with AP1189, 100 mg dose after 12 completed subjects on AP1189, 50 mg, and to reduce the sample size in the (100 mg) group of Part 1 from 18 down to a minimum of 12 subjects (protocol version 7.0).
22 September 2020	Amendment 4 concerned the determination of melanocortin receptor type 1 (MC1r) variants in subjects randomized to treatment by analyzing a tissue sample using RT-PCR (Reverse transcription-polymerase chain reaction (RT-PCR can be used, for example, to enable molecular cloning, sequencing, or simple detection of RNA)) (protocol version 8.0).
27 January 2021	Amendment 4 concerned adding a sub-study in Bulgaria and Moldova to the clinical study protocol. The purpose of the sub-study was to investigate if the effect of AP1189 in newly diagnosed subjects with severe rheumatoid arthritis who were to start up-titration with methotrexate was comparable in these two countries compared to the main study (protocol version 9.0)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported