



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