Clinical trial results:
EXploratory PLatform trial on Anti-INflammatory agents in Alzheimer's Disease (EXPLAIN-AD): A randomized, placebo-controlled, multicenter platform study to evaluate the efficacy, safety, tolerability and pharmacokinetics of various anti-inflammatory agents in patients with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease

Summary

EudraCT number	2020-003966-38
Trial protocol	FI IS
Global end of trial date	07 March 2024

Results information

Result version number	v1
This version publication date	21 March 2025
First version publication date	21 March 2025

Trial information

Trial identification

Sponsor protocol code	CADPT06A12201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04795466
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.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	07 March 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 March 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the effects of each individual agent vs placebo on cognition in early Alzheimer's Disease using the Neuropsychological Test Battery (NTB) score at 24 weeks.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Symptomatic treatments for AD (such as ChEIs or memantine) could be continued, in addition to the investigational treatment; however, dosage should not be adjusted in the 3 months preceding baseline and for the duration of the study. Following randomization, the investigator had to avoid initiating a symptomatic treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 October 2021
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	Finland: 4
Country: Number of subjects enrolled	Iceland: 12
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	34
EEA total number of subjects	16

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	4
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 10 sites in 4 different countries

Pre-assignment

Screening details:

There was a screening period (Day -60 to Day -8), followed by a baseline period of 7 days (Day -7 to Day -1), before first treatment.

34 participants were enrolled and received study treatment (safety analysis set). One participant was misdiagnosed with AD and was excluded from pharmacodynamic analysis set.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Canakinumab

Arm description:

Canakinumab 150 mg SC once every 4 weeks for the first 2 doses followed by 300 mg SC once every 4 weeks for the subsequent 4 doses.

Arm type	Experimental
Investigational medicinal product name	Canakinumab
Investigational medicinal product code	ACZ885
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Canakinumab 150 mg SC once every 4 weeks for the first 2 doses followed by 300 mg SC once every 4 weeks for the subsequent 4 doses.

Arm title	Placebo

Arm description:

Matching placebo subcutaneous injections

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo sub-cutaneous injections

Number of subjects in period 1	Canakinumab	Placebo
Started	16	18
Pharmacodynamic analysis set	15	18
Completed	10	16
Not completed	6	2
Physician decision	1	-
Consent withdrawn by subject	2	1
Adverse event, non-fatal	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Canakinumab
Reporting group description:	
Canakinumab 150 mg SC once every 4 weeks for the first 2 doses followed by 300 mg SC once every 4 weeks for the subsequent 4 doses.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo subcutaneous injections	

Reporting group values	Canakinumab	Placebo	Total
Number of subjects	16	18	34
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	3	5
From 65-84 years	14	15	29
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	71	72.4	
standard deviation	± 6.53	± 6.71	-
Sex: Female, Male			
Units: Participants			
Female	3	8	11
Male	13	10	23
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	16	18	34
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	16	18	34
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Canakinumab
Reporting group description:	
Canakinumab 150 mg SC once every 4 weeks for the first 2 doses followed by 300 mg SC once every 4 weeks for the subsequent 4 doses.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo subcutaneous injections	

Primary: Change from baseline in cognition as measured by the Neuropsychological Test Battery (NTB) z-scores

End point title	Change from baseline in cognition as measured by the Neuropsychological Test Battery (NTB) z-scores
End point description:	
NTB is a composite of multiple neuropsychological tests that provide a thorough assessment of the cognitive domains affected by early Alzheimer's Disease (AD), in particular, memory, executive function, attention and verbal fluency. 5 out of 9 NTB components were administered in the study, Rey Auditory Verbal Learning Test (RAVLT) immediate and delayed scores, Wechsler Memory Scale Digit Span, Controlled Word Association Test (COWAT) and Category Fluency Test (CFT). For each component a raw score was converted to z-score that indicates the number of standard deviations away from the mean. Total Z-score was derived by averaging all resulting z-scores. A change from baseline was calculated as post-baseline z-score minus pre-treatment z-score. A zero Z-score means no cognitive change, a negative value indicates decline, and a positive value means improvement.	
End point type	Primary
End point timeframe:	
Baseline and day 171	

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	16		
Units: z-score change from baseline				
least squares mean (standard error)	0.225 (± 0.116)	0.156 (± 0.0905)		

Statistical analyses

Statistical analysis title	NTB Total z-score - day 171
Comparison groups	Canakinumab v Placebo

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6386
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	0.069
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.178
upper limit	0.316
Variability estimate	Standard error of the mean
Dispersion value	0.1442

Secondary: Change from baseline in memory as measured by the total composite NTB memory z-score

End point title	Change from baseline in memory as measured by the total composite NTB memory z-score

End point description:

Total Neuropsychological Test Battery memory composite score is a "memory function" score composed of the NTB RAVLT immediate and delayed scores.
For each component a raw score was converted to z-score that indicates the number of standard deviations away from the mean. Total Z-score was derived by averaging the two resulting z-scores. A change from baseline was calculated as post-baseline z-score minus pre-treatment z-score. A zero Z-score means no cognitive change, a negative value indicates decline, and a positive value means improvement.

End point type	Secondary

End point timeframe:

Baseline and day 171

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	16		
Units: z-score change from baseline				
least squares mean (standard error)	0.461 (± 0.1382)	0.463 (± 0.1062)		

Statistical analyses

Statistical analysis title	Memory function - day 171
Comparison groups	Canakinumab v Placebo

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9917
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	-0.002
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.3
upper limit	0.296
Variability estimate	Standard error of the mean
Dispersion value	0.1739

Secondary: Change from baseline in digit symbol substitution test (DSST) score - CANTAB

End point title	Change from baseline in digit symbol substitution test (DSST) score - CANTAB

End point description:

The DSST is an attention-demanding component of the Wechsler Adult Intelligence Scale-IV.
The DSST score is the number of digits coded correctly in a fixed amount of time. The DSST has a minimum of "0" correct responses and does not have a maximum; a higher number on the DSST represents better performance

The test was administered using CANTAB web based testing

End point type	Secondary

End point timeframe:

Baseline and day 171

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	16		
Units: DSST score change from baseline				
least squares mean (standard error)	1.96 (± 1.37)	2.45 (± 1.13)		

Statistical analyses

Statistical analysis title	DSST - day 171
Comparison groups	Canakinumab v Placebo

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.787
Method	Mixed models analysis
Parameter estimate	Repeated measures analysis
Point estimate	-0.49
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.56
upper limit	2.58
Variability estimate	Standard error of the mean
Dispersion value	1.8

Secondary: Change from baseline in executive function as measured by the total composite NTB executive function z-score

End point title	Change from baseline in executive function as measured by the total composite NTB executive function z-score

End point description:

The total Neuropsychological Test Battery executive function composite score is an "executive function" score composed of the NTB Wechsler Memory Scale Digit Span, COWAT, and CFT.
For each component a raw score was converted to z-score that indicates the number of standard deviations away from the mean. Total Z-score was derived by averaging the two resulting z-scores. A change from baseline was calculated as post-baseline z-score minus pre-treatment z-score. A zero Z-score means no cognitive change, a negative value indicates decline, and a positive value means improvement.

End point type	Secondary

End point timeframe:

Baseline and day 171

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	16		
Units: z-score change from baseline				
least squares mean (standard error)	0.111 (± 0.1492)	-0.075 (± 0.1251)		

Statistical analyses

Statistical analysis title	Executive function- day 171
Comparison groups	Canakinumab v Placebo

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.351
Method	Mixed models analysis
Parameter estimate	least squares mean difference
Point estimate	0.186
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.148
upper limit	0.52
Variability estimate	Standard error of the mean
Dispersion value	0.1958

Secondary: Change from baseline in neuropsychiatric symptoms associated distress as measured by the Neuropsychiatric Inventory caregiver distress (NPI-D) score

End point title	Change from baseline in neuropsychiatric symptoms associated distress as measured by the Neuropsychiatric Inventory caregiver distress (NPI-D) score

End point description:

Neuropsychiatric Inventory (NPI) total score is globally recognized and the most frequently used assessment of neuropsychiatric symptoms in AD trials. NPI covers twelve neuropsychiatric domains. For each domain there are four scores, frequency (rated 1-4), severity (rated 1-3), domain total score (frequency x severity) and caregiver distress score (rated 0-5).
The caregiver distress score (NPI-D) was calculated by adding together the scores of the 12 individual NPI distress questions, and ranges from 0 to 60, with higher values indicating greater severity.

End point type	Secondary

End point timeframe:

Baseline and day 171

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	16		
Units: NPI-D score change from Baseline				
arithmetic mean (standard deviation)	-2.7 (± 7.70)	1.2 (± 5.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in neuropsychiatric symptoms as measured by the Neuropsychiatric Inventory (NPI) total score

End point title	Change from baseline in neuropsychiatric symptoms as measured by the Neuropsychiatric Inventory (NPI) total score

End point description:

Neuropsychiatric Inventory (NPI) total score is globally recognized and the most frequently used assessment of neuropsychiatric symptoms in AD trials. NPI covers twelve neuropsychiatric domains. For each domain there are four scores, frequency (rated 1-4), severity (rated 1-3), domain total score (frequency x severity) and caregiver distress score (rated 0-5).
The NPI total score was calculated by adding 12 domain total scores together, and ranges from 0 to 144, with higher values indicating greater severity.

End point type	Secondary

End point timeframe:

Baseline and day 171

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	16		
Units: NPI total score change from Baseline				
arithmetic mean (standard deviation)	-1.4 (± 7.76)	2.9 (± 8.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Mean eNeuropsychiatric at home caregiver assessment score

End point title	Change from baseline in Mean eNeuropsychiatric at home caregiver assessment score

End point description:

Neuropsychiatric Inventory (NPI) total score is globally recognized and the most frequently used assessment of neuropsychiatric symptoms in AD trials. NPI covers twelve neuropsychiatric domains. For each domain there are four scores, frequency (rated 1-4), severity (rated 1-3), domain total score (frequency x severity) and caregiver distress score (rated 0-5).
The eNeuropsychiatric at-home assessment was calculated the same way as the in-clinic NPI by adding the12 domain total scores together. The eNeuropsychiatric at-home assessments were completed more frequently than the single time-point in-clinic NPI assessment and the scores averaged. It ranges from 0 to 144, with higher values indicating greater severity.

End point type	Secondary

End point timeframe:

Baseline, day 85

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: eNeuropsychiatric change from Baseline				
arithmetic mean (standard deviation)	0.983 (± 3.7904)	-1.094 (± 1.7083)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Everyday Cognition scale (ECog) total score

End point title	Change from baseline in Everyday Cognition scale (ECog) total score

End point description:

Everyday Cognition (ECog) scale measures cognitively-relevant everyday abilities and is comprised of 39 items covering six cognitively-relevant domains: Everyday Memory, Everyday Language, Everyday Visuospatial Abilities, Everyday Planning, Everyday Organization, and Everyday Divided Attention. Each item is scored on a 4 point scale (1=better or no change compared to 10 years earlier, 2=questionable/occasionally worse, 3=consistently a little worse, 4=consistently much worse). An "I don't know" response is also included, in that case the item is not included in the calculation.
The total ECog score is calculated as the sum of all 39 items, and ranges from 0 to 156. Lower total ECog scores indicate better performance.

End point type	Secondary

End point timeframe:

Baseline and day 171

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	16		
Units: ECog total score change from Baseline				
arithmetic mean (standard deviation)	1.2 (± 14.26)	3.4 (± 11.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in eCognitive testing scores - MTS proportional slowing 8-2 patterns

End point title	Change from baseline in eCognitive testing scores - MTS proportional slowing 8-2 patterns

End point description:

Match to Sample Visual Search (MTS) assesses attention and visual searching, with a speed accuracy trade-off. The participant is shown a complex visual pattern in the middle of the screen. After a brief delay, a varying number of similar patterns are shown in a circle of boxes around the edge of the screen. Only one of these patterns matches the pattern in the center of the screen, and the participant must indicate which it is by selecting it.
MTS proportional slowing 8-2 patterns is the difference in mean time between presentation of the response stimulus options and the subject selecting the correct box on their first attempt on the 8 pattern assessment trials compared to the 2 pattern assessment trials. It starts at 0 without a maximum limit, and with higher scores indicating a worse outcome.

End point type	Secondary

End point timeframe:

Baseline, day 85

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	12		
Units: Change from baseline in milliseconds				
arithmetic mean (standard deviation)	143.780 (± 2871.0641)	77.573 (± 2824.3325)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in eCognitive testing scores - SWM strategy

End point title	Change from baseline in eCognitive testing scores - SWM strategy

End point description:

Spatial Working Memory (SWM) is a test of the subject's ability to retain spatial information and to manipulate remembered items in working memory. A trial begins with several colored squares (boxes) being shown on the screen. The overall aim is that the subject should find a blue 'token' in each of the boxes and use them to fill up an empty column. The subject must touch each box in turn until one opens with a blue 'token' inside (a search). Returning to an empty box already sampled on this search is an error.
SWM Strategy is the number of times a subject begins a new search pattern from the same box they started with previously. If they always begin a search from the same starting point, we infer that the subject is employing a planned strategy for finding the tokens. SMW strategy ranges from 3 to 26, a low score indicates high strategy use, they always begin the search from the same box, and a high score indicates that they are beginning their searches from many different boxes.

End point type	Secondary

End point timeframe:

Baseline, day 85

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	12		
Units: SWM strategy change from baseline				
arithmetic mean (standard deviation)	-0.28 (± 1.149)	-0.92 (± 1.459)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in eCognitive testing scores - SWM between errors

End point title	Change from baseline in eCognitive testing scores - SWM between errors

End point description:

Spatial Working Memory (SWM) is a test of the subject's ability to retain spatial information and to manipulate remembered items in working memory. A trial begins with several colored squares (boxes) being shown on the screen. The overall aim is that the subject should find a blue 'token' in each of the boxes and use them to fill up an empty column. The subject must touch each box in turn until one opens with a blue 'token' inside (a search). Returning to an empty box already sampled on this search is an error.
SWM between errors is the number of times the subject incorrectly revisits a box in which a token has previously been found. It starts at 0 without a maximum limit with higher scores indicating a worse outcome.

End point type	Secondary

End point timeframe:

Baseline, day 85

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	12		
Units: SWMBE score change from baseline				
arithmetic mean (standard deviation)	-1.56 (± 6.018)	-1.83 (± 4.910)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in microglia activation as measured by Positron-Emission Tomography-Translocator Protein 18kDa - microglia activation

End point title	Change from baseline in microglia activation as measured by Positron-Emission Tomography-Translocator Protein 18kDa - microglia activation

End point description:

Positron-Emission Tomography-Translocator Protein 18kDa-microglia activation (PET TSPO) is considered a marker of central inflammation (a marker for activated microglia and astrocytes) and the signal strength has been shown to correlate with worsening clinical severity in participants with MCI or AD, measures of cognition and various clinical scores. Relative % change from baseline in volume of distribution (Vt) of the radio tracer for TSPO after treatment.

Since only one participant completed day 85 PET TSPO, no data is reported here in order to protect and maintain participant privacy/confidentiality.

End point type	Secondary

End point timeframe:

Baseline and day 85

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: Percent change from baseline				
arithmetic mean (standard deviation)	()	()		

Notes:

[1] - No data is reported here in order to protect and maintain participant privacy/confidentiality.

[2] - No data is reported here in order to protect and maintain participant privacy/confidentiality.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in eCognitive testing scores - PAL first attempt memory score

End point title	Change from baseline in eCognitive testing scores - PAL first attempt memory score

End point description:

Pair associated learning (PAL): tests participants' visual memory/new learning using patterns randomly displayed in boxes on a screen. Participants are to touch the box where patterns first appeared.
PAL first attempt memory score is the number of times a subject choses the correct box on their first attempt when recalling the pattern locations. Ranges from 0 to 20 with higher score indicates a better outcome.

End point type	Secondary

End point timeframe:

Baseline, day 85

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	12		
Units: PAL score change from baseline				
arithmetic mean (standard deviation)	-0.17 (± 2.716)	0.08 (± 3.059)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum pharmacokinetic concentrations of Canakinumab

End point title	Serum pharmacokinetic concentrations of Canakinumab[3]

End point description:

Serum pharmacokinetic pre-dose concentrations of CanakinumabConcentrations below the LLOQ were reported as "zero".

End point type	Secondary

End point timeframe:

Baseline, day29, day 57, day 8, day 141, day 171

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic concentration of the active drug can only be reported for the active drug per definition. We cannot report concentrations of placebo arm.

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline (n=14)	0.0 (± 0.00)			
Day 29 (n=16)	8921.3 (± 2721.47)			
Day 57 (n=13)	14230.8 (± 4712.07)			
Day 85 (n=12)	26575.0 (± 10216.93)			
Day 141 (n=11)	34000.0 (± 11288.67)			
Day 171 (n=10)	33170.0 (± 6825.45)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total target (IL-1 beta) concentration in serum and CSF

End point title	Total target (IL-1 beta) concentration in serum and CSF

End point description:

Serum and CSF samples were obtained and evaluated for total target concentrations (the sum of free and drug-bound target) as a pharmacodynamic (PD) marker for target engagement.

End point type	Secondary

End point timeframe:

Baseline, day 29, day 57, day 85, day 141, day 171 for serum concentrations and Baseline and day 85 for CSF concentrations

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	18		
Units: pg/mL				
arithmetic mean (standard deviation)				
Serum - Baseline (n=13 /n=18)	0.000 (± 0.0000)	0.000 (± 0.0000)		
Serum - Day 29 (n=15 /n=18)	12.632 (± 4.4949)	0.000 (± 0.0000)		
Serum - Day 57 (n=13 /n=17)	20.818 (± 10.2918)	0.000 (± 0.0000)		

Serum - Day 85 (n=11 /n=16)	23.291 (± 5.2984)	0.000 (± 0.0000)		
Serum - Day 141 (n=11 /n=16)	44.473 (± 58.3963)	0.000 (± 0.0000)		
Serum - Day 171 (n=10 /n=16)	28.460 (± 18.4483)	0.000 (± 0.0000)		
CSF - Baseline (n=15 /n=18)	0.000 (± 0.0000)	0.000 (± 0.0000)		
CSF - Day 85 (n=12 /n=15)	0.000 (± 0.0000)	0.023 (± 0.0883)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with anti-agent antibodies in serum

End point title	Number of participants with anti-agent antibodies in serum[4]

End point description:

Number of participants with anti-agent antibodies in serum. Immunogenicity (IG) was assessed in serum of all participants treated with biotherapeutic drug.

End point type	Secondary

End point timeframe:

Baseline, day 85, day 171

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Anti-agent antibodies can only be reported for participants receiving the active drug.

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Participants				
Baseline|POSITIVE	0			
Baseline|NEGATIVE	16			
Day 85|POSITIVE	0			
Day 85|NEGATIVE	12			
Day 171|POSITIVE	0			
Day 171|NEGATIVE	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who experience adverse events and serious adverse events

End point title	Number of participants who experience adverse events and serious adverse events

End point description:

Clinically significant abnormalities of laboratory values, physical findings, electrocardiogram findings and

other safety assessments were recorded as adverse events if the findings meet the defined criteria for adverse events.

AE grades to characterize the severity of the AEs were based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5. For CTCAE, Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = death related to AE

End point type	Secondary

End point timeframe:

From first dose up to approximately 140 days post last dose (day 281)

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: Participants				
Participants with at least one AE	14	16		
Participants with grade 1 AEs	14	16		
Participants with grade 2 AEs	6	6		
Participants with grade 3 AEs	1	0		
Participants with study drug related AEs	4	5		
Participants with serious AEs	2	1		
AEs leading to drug discont.	3	1		
Treatment related AEs leading to drug discont.	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose up to approximately 140 days post last dose (day 281)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups	
Reporting group title	ACZ885
Reporting group description:	
ACZ885	
Reporting group title	Total
Reporting group description:	
Total	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	ACZ885	Total	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 16 (12.50%)	3 / 34 (8.82%)	1 / 18 (5.56%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Transitional cell carcinoma			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Metabolic encephalopathy			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			

subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal infection			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	ACZ885	Total	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 16 (81.25%)	29 / 34 (85.29%)	16 / 18 (88.89%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 16 (25.00%)	5 / 34 (14.71%)	1 / 18 (5.56%)
occurrences (all)	4	5	1
Flushing			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Immune system disorders			
Sensitisation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Procedural anxiety			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Persecutory delusion			

subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Irritability			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Confusional state			
subjects affected / exposed	2 / 16 (12.50%)	2 / 34 (5.88%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Anxiety			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Investigations			
White blood cells urine positive			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Weight decreased			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Lipase increased			
subjects affected / exposed	1 / 16 (6.25%)	3 / 34 (8.82%)	2 / 18 (11.11%)
occurrences (all)	1	4	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Blood creatinine increased			
subjects affected / exposed	1 / 16 (6.25%)	3 / 34 (8.82%)	2 / 18 (11.11%)
occurrences (all)	1	3	2
Blood bilirubin increased			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			

Post lumbar puncture syndrome			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Immunisation reaction			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Fall			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Contusion			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Scratch			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Thermal burn			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Dizziness			
subjects affected / exposed	0 / 16 (0.00%)	2 / 34 (5.88%)	2 / 18 (11.11%)
occurrences (all)	0	3	3
Intention tremor			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Syncope			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Headache			

subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Eye disorders			
Cataract			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Dyspepsia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Haemorrhoids			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Inguinal hernia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Pancreatitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Diverticulum			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Abdominal tenderness			

subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Abdominal pain			
subjects affected / exposed	0 / 16 (0.00%)	2 / 34 (5.88%)	2 / 18 (11.11%)
occurrences (all)	0	3	3
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Eczema			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Acne			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	2 / 16 (12.50%)	3 / 34 (8.82%)	1 / 18 (5.56%)
occurrences (all)	2	3	1
Acute kidney injury			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Back pain			
subjects affected / exposed	2 / 16 (12.50%)	4 / 34 (11.76%)	2 / 18 (11.11%)
occurrences (all)	2	4	2
Arthralgia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Infections and infestations			
Asymptomatic bacteriuria			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0

Conjunctivitis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Lower respiratory tract infection			
subjects affected / exposed	2 / 16 (12.50%)	2 / 34 (5.88%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Otitis externa			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Pneumonia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Rhinitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Tonsillitis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 34 (2.94%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 16 (6.25%)	2 / 34 (5.88%)	1 / 18 (5.56%)
occurrences (all)	1	2	1
Urinary tract infection			
subjects affected / exposed	1 / 16 (6.25%)	3 / 34 (8.82%)	2 / 18 (11.11%)
occurrences (all)	1	4	3
Vaginal infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	2	2
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Viral infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 34 (2.94%)	1 / 18 (5.56%)
occurrences (all)	0	2	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2021	The purpose of this amendment is to address comments from the Medicines and Healthcare Products Regulatory Agency (MHRA) including: 1. Revisions to clinically important infection-related safety language in alignment with the administration of immunomodulatory agents; 2. Revisions to female contraception requirement to reflect unknown risks to fetal development in immunomodulatory agents.
01 August 2021	The rationale for this protocol amendment is three-fold: 1. To reflect logistical changes in the study execution prior to enrolling participants 2. To increase the duration of the study when monoclonal antibodies are administered 3. Address previous requests from The Finnish Medicines Agency (FIMEA) and US Food and Drug Administration (FDA) received during the review of the original clinical trial submission. Minor changes were made to some sections of the protocol for additional clarity and better understanding of the study.
01 March 2022	The rationale for this protocol amendment is to update Inclusion/Exclusion section to better specify excluded medications or timing around previous exposure to prohibited medications; and, to more clearly specify the intended population to be studied in the EXPLAIN-AD trial. In addition, this amendment provides an update to SAE section regarding covid-19 in order to align with evolving state of pandemic. Minor changes were made to some sections of the protocol for additional clarity and better understanding of the study.
04 September 2022	The rationale for this protocol amendment is to update Inclusion/Exclusion section to better clarify the targeted participant population based on eligibility with the intention to not unnecessarily exclude participants that are suitable for this trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported