

**Clinical trial results:****A Phase 2a, Randomised, Double-blind, Parallel Study to Assess the Efficacy, Safety and Tolerability of AZD9567 compared to Prednisolone 20 mg in patients with active Rheumatoid Arthritis (RA)****Summary**

EudraCT number	2017-000838-64
Trial protocol	NL DK
Global end of trial date	12 November 2019

Results information

Result version number	v1 (current)
This version publication date	27 September 2020
First version publication date	27 September 2020

Trial information**Trial identification**

Sponsor protocol code	D6470C00003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03368235
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Karlebyhusentren, B674 Astraallen, Södertälje, Sweden, SE-151 85
Public contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.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	Interim
Date of interim/final analysis	06 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 November 2019
Global end of trial reached?	Yes
Global end of trial date	12 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of AZD9567 40 milligram (mg), compared to prednisolone 20 mg in participants with active rheumatoid arthritis (RA) in spite of stable treatment with conventional and/or subcutaneous or intravenous biological disease-modifying anti-rheumatic drugs (DMARDs).

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Sweden: 5
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	15
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a Phase 2a study conducted in participants with active RA in spite of stable treatment with conventional DMARDs at 5 investigational sites across Sweden and The Netherlands between 18 January 2018 and 12 November 2019.

Pre-assignment

Screening details:

A total of 21 participants were randomized in a 1:1 ratio to take either AZD9567 or prednisolone in a 2-week double-blind, double-dummy treatment period.

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, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	AZD9567

Arm description:

Participants received AZD9567 40 mg oral suspension and placebo capsules matching with prednisolone, orally once daily, for 2 weeks.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo capsule matching with prednisolone orally once daily for 2 weeks.

Investigational medicinal product name	AZD9567
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

AZD9567 40 mg oral suspension once daily for 2 weeks.

Arm title	Prednisolone
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Arm description:

Participants received prednisolone 20 mg oral capsules and placebo oral suspension matching with AZD9567, once daily for 2 weeks.

Arm type	Active comparator
Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Prednisolone 20 mg capsule orally once daily for 2 weeks.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Placebo matching with AZD9567 oral suspension once daily for 2 weeks.

Number of subjects in period 1	AZD9567	Prednisolone
Started	11	10
Completed	11	10

Baseline characteristics

Reporting groups

Reporting group title	AZD9567
Reporting group description: Participants received AZD9567 40 mg oral suspension and placebo capsules matching with prednisolone, orally once daily, for 2 weeks.	
Reporting group title	Prednisolone
Reporting group description: Participants received prednisolone 20 mg oral capsules and placebo oral suspension matching with AZD9567, once daily for 2 weeks.	

Reporting group values	AZD9567	Prednisolone	Total
Number of subjects	11	10	21
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)	7	8	15
From 65-84 years	4	2	6
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	64.5	55.5	
standard deviation	± 8.41	± 13.58	-
Sex: Female, Male			
Units: participants			
Female	8	5	13
Male	3	5	8
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	11	10	21
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	11	10	21
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	AZD9567
Reporting group description: Participants received AZD9567 40 mg oral suspension and placebo capsules matching with prednisolone, orally once daily, for 2 weeks.	
Reporting group title	Prednisolone
Reporting group description: Participants received prednisolone 20 mg oral capsules and placebo oral suspension matching with AZD9567, once daily for 2 weeks.	

Primary: Least Square (LS) Mean Change From Baseline in 28 Joint Disease Activity Score Using C-Reactive Protein (DAS28-CRP) at Day 15

End point title	Least Square (LS) Mean Change From Baseline in 28 Joint Disease Activity Score Using C-Reactive Protein (DAS28-CRP) at Day 15
End point description: The DAS28-CRP is a measure of disease activity in RA. The score includes the number of tender and swollen joints (out of 28), CRP level (a measure of inflammation in the blood), and the patient's global assessment (PGA) of health (ranging from very well to very poor). The DAS28-CRP was derived as follows: $0.56 \times \sqrt{[\text{tender joint count 28 (TJC28)}]} + 0.28 \times \sqrt{[\text{swollen joint count 28 (SJC28)}]} + 0.014 \times \text{global health (GH)} + 0.36 \times \text{Ln}(\text{CRP}+1) + 0.96$ to produce the overall DAS28-CRP score on a scale ranged from 0-10 with higher score indicating worse RA symptoms. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) prior to the first dose of study treatment. The Full analysis set (FAS) included all participants who were randomized and received at least 1 dose of study treatment.	
End point type	Primary
End point timeframe: Baseline (Day 1) and Day 15	

End point values	AZD9567	Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: score on a scale				
least squares mean (standard error)	-1.931 (\pm 0.3460)	-2.403 (\pm 0.3373)		

Statistical analyses

Statistical analysis title	Treatment comparison: AZD9567 Vs prednisolone
Statistical analysis description: MMRM = mixed model repeated measures.	
Comparison groups	AZD9567 v Prednisolone

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.315 ^[1]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.472
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.487
upper limit	1.431
Variability estimate	Standard error of the mean
Dispersion value	0.4569

Notes:

[1] - Based on MMRM model with the baseline DAS28-CRP score as a continuous covariate and country, visit and treatment group as categorical fixed effects, as well as visit interaction with treatment group, using unstructured covariance matrix.

Secondary: Percentage of Participants Achieving American College of Rheumatology (ACR) 20, ACR50 and ACR70 Responses

End point title	Percentage of Participants Achieving American College of Rheumatology (ACR) 20, ACR50 and ACR70 Responses
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End point description:

The ACR20, ACR50 or ACR70 was achieved if there was at least a 20%, 50% or 70% improvement from baseline in swollen joint count 66 (SJC66) and tender joint count 68 (TJC68) and 3 or more of the 5 following assessments: participant's assessment of pain, GH, physician's global assessment of disease activity, participant's assessment of physical function and CRP. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) prior to the first dose of study treatment. The FAS included all participants who were randomized and received at least 1 dose of study treatment. Participants with missing ACR assessment at Day 15 were considered as non-responders in the respective analysis.

End point type	Secondary
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End point timeframe:

Day 15

End point values	AZD9567	Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: percentage of participants				
number (not applicable)				
ACR20	63.6	70.0		
ACR50	36.4	70.0		
ACR70	18.2	50.0		

Statistical analyses

Statistical analysis title	Treatment comparison ACR20:AZD9567 Vs prednisolone
Comparison groups	AZD9567 v Prednisolone

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.807 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.807
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	5.34

Notes:

[2] - Logistic regression model with the treatment group, country and baseline DAS28-CRP as covariate.

Statistical analysis title	Treatment comparison ACR70:AZD9567 Vs prednisolone
Comparison groups	AZD9567 v Prednisolone
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.183
Method	Fisher exact

Statistical analysis title	Treatment comparison ACR50:AZD9567 Vs prednisolone
Comparison groups	AZD9567 v Prednisolone
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.198
Method	Fisher exact

Secondary: LS Mean Change From Baseline in SJC66 Score at Day 15

End point title	LS Mean Change From Baseline in SJC66 Score at Day 15
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End point description:

A total of 66 joints (33 left, 33 right) were evaluated for swelling. The swollen joint count represents the number of joints in which there was synovial fluid and or soft tissue swelling, but not if bony overgrowth was found. A swollen joint was scored as 0 (absent) and 1 (present) for each joint. The SJC66 was calculated as sum of swollen joints with present status on electronic case report form (eCRF). The swollen joint count ranged from 0-66 with higher score indicating disease severity. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) prior to the first dose of study treatment. The FAS included all participants who were randomized and received at least 1 dose of study treatment.

End point type	Secondary
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End point timeframe:

Baseline and Day 15

End point values	AZD9567	Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: score on a scale				
least squares mean (standard error)	-6.24 (± 0.894)	-6.66 (± 0.860)		

Statistical analyses

Statistical analysis title	Treatment comparison: AZD9567 Vs prednisolone
Comparison groups	AZD9567 v Prednisolone
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.717 ^[3]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.98
upper limit	2.81
Variability estimate	Standard error of the mean
Dispersion value	1.136

Notes:

[3] - The MMRM with the baseline SJC66 score as a continuous covariate and country, visit and treatment group as categorical fixed effects, as well as visit interaction with treatment group, using unstructured covariance matrix.

Secondary: LS Mean Change From Baseline in TJC68 Score at Day 15

End point title	LS Mean Change From Baseline in TJC68 Score at Day 15
End point description:	A total of 68 joints (34 left, 34 right) were evaluated for tenderness. The tender joint count represents the number of joints in which pain was reported. A tender joint was scored as 0 (absent) and 1 (present) for each joint. The TJC68 was calculated as sum of tender joints with present status on eCRF. The tender joint count ranged from 0-68 with higher score indicating disease severity. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) prior to the first dose of study treatment. The FAS included all participants who were randomized and received at least 1 dose of study treatment.
End point type	Secondary
End point timeframe:	Baseline and Day 15

End point values	AZD9567	Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: score on a scale				
least squares mean (standard error)	-9.02 (± 2.463)	-7.90 (± 2.362)		

Statistical analyses

Statistical analysis title	Treatment comparison: AZD9567 Vs prednisolone
Comparison groups	AZD9567 v Prednisolone
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.724 ^[4]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.69
upper limit	5.46
Variability estimate	Standard error of the mean
Dispersion value	3.115

Notes:

[4] - The MMRM with the baseline TJC68 score as a continuous covariate and country, visit and treatment group as categorical fixed effects, as well as visit interaction with treatment group, using unstructured covariance matrix.

Secondary: LS Mean Change From Baseline in TJC28 Score at Day 15

End point title	LS Mean Change From Baseline in TJC28 Score at Day 15
End point description:	TJC28 was evaluated as one of the components that comprised the DAS28-score. A total of 28 joints (14 left, 14 right) were evaluated for tenderness as obtained from the joint count right or left eCRF. The tender joint count represents the number of joints in which pain was reported. A tender joint was scored as 0 (absent) and 1 (present) for each joint. The TJC28 was calculated as sum of tender joints with present status on eCRF. The tender joint count ranged from 0-28 with higher score indicating disease severity. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) prior to the first dose of study treatment. The FAS included all participants who were randomized and received at least 1 dose of study treatment.
End point type	Secondary
End point timeframe:	Baseline and Day 15

End point values	AZD9567	Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: score on a scale				
least squares mean (standard error)	-6.12 (\pm 1.251)	-6.07 (\pm 1.208)		

Statistical analyses

Statistical analysis title	Treatment comparison: AZD9567 Vs prednisolone
Comparison groups	AZD9567 v Prednisolone
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.973 ^[5]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.43
upper limit	3.32
Variability estimate	Standard error of the mean
Dispersion value	1.6

Notes:

[5] - The MMRM with the baseline TJC28 score as a continuous covariate and country, visit and treatment group as categorical fixed effects, as well as visit interaction with treatment group, using unstructured covariance matrix.

Secondary: LS Mean Change From Baseline in SJC28 Score at Day 15

End point title	LS Mean Change From Baseline in SJC28 Score at Day 15
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End point description:

SJC28 was evaluated as one of the components that comprised the DAS28-score. A total of 28 joints (14 left, 14 right) were evaluated for swelling as obtained from the joint count right or left eCRF. The swollen joint count represents the number of joints in which there was synovial fluid and or soft tissue swelling, but not if bony overgrowth was found. A swollen joint was scored as 0 (absent) and 1 (present) for each joint. The SJC28 was calculated as sum of swollen joints with present status on eCRF. The swollen joint count ranged from 0-28 with higher score indicating disease severity. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) prior to the first dose of study treatment. The FAS included all participants who were randomized and received at least 1 dose of study treatment.

End point type	Secondary
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End point timeframe:

Baseline and Day 15

End point values	AZD9567	Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: score on a scale				
least squares mean (standard error)	-5.14 (\pm 0.653)	-5.40 (\pm 0.628)		

Statistical analyses

Statistical analysis title	Treatment comparison: AZD9567 Vs prednisolone
Comparison groups	AZD9567 v Prednisolone
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.757 ^[6]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	2.03
Variability estimate	Standard error of the mean
Dispersion value	0.837

Notes:

[6] - The MMRM with the baseline SJC28 score as a continuous covariate and country, visit and treatment group as categorical fixed effects, as well as visit interaction with treatment group, using unstructured covariance matrix.

Secondary: LS Mean Change From Baseline in GH Score at Day 15

End point title	LS Mean Change From Baseline in GH Score at Day 15
End point description:	GH was evaluated as one of the components that comprised the DAS28-score. Participant's GH was measured using PGA of disease activity by means of the visual analogue scale (VAS). The PGA VAS consists of a 100 millimeter (mm) long scale ranging from 0 (very well) to 100 (very poor). Higher score indicated greater disease severity. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) prior to the first dose of study treatment. The FAS included all participants who were randomized and received at least 1 dose of study treatment.
End point type	Secondary
End point timeframe:	Baseline and Day 15

End point values	AZD9567	Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: score on a scale				
least squares mean (standard error)	-27.7 (\pm 7.26)	-37.4 (\pm 7.11)		

Statistical analyses

Statistical analysis title	Treatment comparison: AZD9567 Vs prednisolone
Comparison groups	AZD9567 v Prednisolone
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.325 [7]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	9.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	30.1
Variability estimate	Standard error of the mean
Dispersion value	9.67

Notes:

[7] - The MMRM with the baseline GH score as a continuous covariate and country, visit and treatment group as categorical fixed effects, as well as visit interaction with treatment group, using unstructured covariance matrix.

Secondary: LS Mean Change From Baseline in CRP at Day 15

End point title	LS Mean Change From Baseline in CRP at Day 15
End point description:	CRP was evaluated as one of the components that comprised the DAS28-score. The CRP was collected at the local laboratory during screening and central laboratory on Days 1, 8, 15 and 28. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) prior to the first dose of study treatment. The FAS included all participants who were randomized and received at least 1 dose of study treatment.
End point type	Secondary
End point timeframe:	Baseline and Day 15

End point values	AZD9567	Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: mg per liter (L)				
least squares mean (standard error)	-10.830 (\pm 2.4207)	-15.586 (\pm 2.5245)		

Statistical analyses

Statistical analysis title	Treatment comparison: AZD9567 Vs prednisolone
Comparison groups	AZD9567 v Prednisolone
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.187 [8]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	4.756
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.514
upper limit	12.025
Variability estimate	Standard error of the mean
Dispersion value	3.4725

Notes:

[8] - The MMRM with the baseline CRP score as a continuous covariate and country, visit and treatment group as categorical fixed effects, as well as visit interaction with treatment group, using unstructured covariance matrix.

Secondary: LS Mean Change From Baseline in Participant's Assessment of Pain Score at Day 15

End point title	LS Mean Change From Baseline in Participant's Assessment of Pain Score at Day 15
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End point description:

Participant's assessment of pain score was evaluated as one of the components that comprised the ACR. Participant's assessment of pain score was assessed from the amount of pain due to RA on a VAS ranging from 0 (no pain) to 100 (extreme pain). Higher score indicated greater disease severity. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) prior to the first dose of study treatment. The FAS included all participants who were randomized and received at least 1 dose of study treatment.

End point type	Secondary
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End point timeframe:

Baseline and Day 15

End point values	AZD9567	Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: score on a scale				
least squares mean (standard error)	-27.3 (± 8.17)	-43.4 (± 7.71)		

Statistical analyses

Statistical analysis title	Treatment comparison: AZD9567 Vs prednisolone
Comparison groups	AZD9567 v Prednisolone
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.144 [9]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	38.1
Variability estimate	Standard error of the mean
Dispersion value	10.49

Notes:

[9] - The MMRM with the baseline participant's assessment of pain score as a continuous covariate and country, visit and treatment group as categorical fixed effects, as well as visit interaction with treatment group, using unstructured covariance matrix.

Secondary: LS Mean Change From Baseline in Physician's Global Assessment of Disease Activity Score at Day 15

End point title	LS Mean Change From Baseline in Physician's Global Assessment of Disease Activity Score at Day 15
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End point description:

Physician's global assessment of disease activity score was evaluated as one of the components that comprised the ACR. The physician's global assessment of disease activity was measured on a VAS ranging from 0 (very well) to 100 (very poor). Higher score indicated greater disease severity. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) prior to the first dose of study treatment. The FAS included all participants who were randomized and received at least 1 dose of study treatment.

End point type	Secondary
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End point timeframe:

Baseline and Day 15

End point values	AZD9567	Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: score on a scale				
least squares mean (standard error)	-37.0 (± 4.38)	-40.9 (± 4.30)		

Statistical analyses

Statistical analysis title	Treatment comparison: AZD9567 Vs prednisolone
Comparison groups	AZD9567 v Prednisolone
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.512 ^[10]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.3
upper limit	16
Variability estimate	Standard error of the mean
Dispersion value	5.73

Notes:

[10] - The MMRM with the baseline disease activity score as a continuous covariate and country, visit and treatment group as categorical fixed effects, as well as visit interaction with treatment group, using unstructured covariance matrix.

Secondary: LS Mean Change From Baseline in Participant's Assessment of Physical Function Score at Day 15

End point title	LS Mean Change From Baseline in Participant's Assessment of Physical Function Score at Day 15
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End point description:

Participant's assessment of physical function score was evaluated as one of the components that comprised the ACR. The participant's assessment of physical function across 8 functional areas was measured by health assessment questionnaire. The total score ranging from 0 (no difficulty) to 24 (inability to perform tasks). Higher score indicated greater disease severity. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) prior to the first dose of study treatment. The FAS included all participants who were randomized and received at least 1 dose of study treatment.

End point type	Secondary
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End point timeframe:

Baseline and Day 15

End point values	AZD9567	Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: score on a scale				
least squares mean (standard error)	-0.441 (± 0.1758)	-0.571 (± 0.1712)		

Statistical analyses

Statistical analysis title	Treatment comparison: AZD9567 Vs prednisolone
Comparison groups	AZD9567 v Prednisolone
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.589 ^[11]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.131
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.631
Variability estimate	Standard error of the mean
Dispersion value	0.2381

Notes:

[11] - The MMRM with the baseline physical function score as a continuous covariate and country, visit and treatment group as categorical fixed effects, as well as visit interaction with treatment group, using unstructured covariance matrix.

Secondary: Area Under the Plasma Concentration-Time Curve Until the Last Quantifiable Concentration (AUClast) of AZD9567

End point title	Area Under the Plasma Concentration-Time Curve Until the Last Quantifiable Concentration (AUClast) of AZD9567 ^[12]
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End point description:

The AUClast was determined using non-compartmental method and calculated using the linear trapezoidal rule when concentrations were increased and the logarithmic trapezoidal rule when concentrations were decreased. The Pharmacokinetic (PK) analysis set included all participants with at least 1 quantifiable AZD9567 concentration with a documented related dosing history.

End point type	Secondary
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End point timeframe:

Predose and 0.25, 0.5, 1, 1.5, 2, 3, 4 and 6 hour postdose on Day 15.

Notes:

[12] - 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: This endpoint was only assessed in participants randomized to AZD9567 reporting group.

End point values	AZD9567			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: hour*nanomole per L (h*nmol/L)				
geometric mean (geometric coefficient of variation)	17800 (± 35.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve From Time Zero to 6 Hours After Dose (AUC0-6) of AZD9567

End point title	Area Under the Concentration-Time Curve From Time Zero to 6 Hours After Dose (AUC0-6) of AZD9567 ^[13]
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End point description:

The AUC0-6 was determined using non-compartmental method and calculated using the linear trapezoidal rule when concentrations were increased and the logarithmic trapezoidal rule when concentrations were decreased. The PK analysis set included all participants with at least 1 quantifiable AZD9567 concentration with a documented related dosing history.

End point type	Secondary
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End point timeframe:

Predose and 0.25, 0.5, 1, 1.5, 2, 3, 4 and 6 hour postdose on Day 15.

Notes:

[13] - 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: This endpoint was only assessed in participants randomized to AZD9567 reporting group.

End point values	AZD9567			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: h*nmol/L				
geometric mean (geometric coefficient of variation)	17740 (\pm 35.34)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of AZD9567

End point title	Maximum Observed Plasma Concentration (Cmax) of
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End point description:

The Cmax of AZD9567 was determined using non-compartmental method. The PK analysis set included all participants with at least 1 quantifiable AZD9567 concentration with a documented related dosing history.

End point type	Secondary
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End point timeframe:

Predose and 0.25, 0.5, 1, 1.5, 2, 3, 4 and 6 hour postdose on Day 15.

Notes:

[14] - 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: This endpoint was only assessed in participants randomized to AZD9567 reporting group.

End point values	AZD9567			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: nmol/L				
geometric mean (geometric coefficient of variation)	4468 (\pm 26.89)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Plasma Concentration (tmax) of AZD9567

End point title	Time to Reach Maximum Plasma Concentration (tmax) of AZD9567 ^[15]
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End point description:

The tmax of AZD9567 was determined using non-compartmental method. The PK analysis set included all participants with at least 1 quantifiable AZD9567 concentration with a documented related dosing history.

End point type	Secondary
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End point timeframe:

Predose and 0.25, 0.5, 1, 1.5, 2, 3, 4 and 6 hour postdose on Day 15.

Notes:

[15] - 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: This endpoint was only assessed in participants randomized to AZD9567 reporting group.

End point values	AZD9567			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: hour				
median (full range (min-max))	0.67 (0.33 to 1.03)			

Statistical analyses

No statistical analyses for this end point

Secondary: Last Plasma Concentration Measured Before the Last Dose (Ctough) of AZD9567

End point title	Last Plasma Concentration Measured Before the Last Dose (Ctough) of AZD9567 ^[16]
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End point description:

The Ctrough of AZD9567 was determined using non-compartmental method before the last dose on Day 15. The PK analysis set included all participants with at least 1 quantifiable AZD9567 concentration with a documented related dosing history. 99999 = not calculable due to a zero predose value.

End point type Secondary

End point timeframe:

Predose on Day 15

Notes:

[16] - 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: This endpoint was only assessed in participants randomized to AZD9567 reporting group.

End point values	AZD9567			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: nmol/L				
geometric mean (geometric coefficient of variation)	99999 (\pm 95.67)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first administration of study treatment (Day 1) up to 2 weeks after last administration of study treatment, approximately 28 days.

Adverse event reporting additional description:

The Safety analysis set included all participants who were randomized and received at least 1 dose of study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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Reporting groups

Reporting group title	AZD9567
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Reporting group description:

Participants received AZD9567 40 mg oral suspension and placebo capsules matching with prednisolone, orally once daily, for 2 weeks.

Reporting group title	Prednisolone
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Reporting group description:

Participants received prednisolone 20 mg oral capsules and placebo oral suspension matching with AZD9567, once daily for 2 weeks.

Serious adverse events	AZD9567	Prednisolone	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Depression suicidal			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	AZD9567	Prednisolone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 11 (90.91%)	9 / 10 (90.00%)	
Vascular disorders			

Haematoma subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 10 (10.00%) 1	
Hot flush subjects affected / exposed occurrences (all)	3 / 11 (27.27%) 3	0 / 10 (0.00%) 0	
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	3 / 11 (27.27%) 3	0 / 10 (0.00%) 0	
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
Peripheral swelling subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 10 (10.00%) 1	
Thirst subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 10 (10.00%) 1	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2	1 / 10 (10.00%) 1	
Dyspnoea subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 10 (10.00%) 1	
Psychiatric disorders			
Agitation subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
Confusional state subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	

Insomnia			
subjects affected / exposed	2 / 11 (18.18%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Mood swings			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Stress			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Head injury			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 11 (18.18%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Restless legs syndrome			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye irritation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Eye pain			

subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 3	0 / 10 (0.00%) 0	
Periorbital swelling subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 10 (10.00%) 1	
Vision blurred subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 3	0 / 10 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
Dry mouth subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2	0 / 10 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
Oral discomfort subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 10 (10.00%) 1	
Stomatitis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Dry skin subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 10 (10.00%) 1	
Erythema subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 10 (10.00%) 1	
Skin atrophy			

subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
Renal and urinary disorders Renal colic subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
Musculoskeletal and connective tissue disorders Costochondritis subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0 0 / 11 (0.00%) 0	1 / 10 (10.00%) 1 1 / 10 (10.00%) 1	
Infections and infestations Eye infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all) Respiratory tract infection viral subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0	0 / 10 (0.00%) 0 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1	
Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 10 (10.00%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2017	Modification of AZD9567 dose from 80 to 40 mg.
19 March 2019	Increase in number of sites from 4-6 to maximum of 10. Addition of erythrocyte sedimentation rate under laboratory (hematology) assessments. Amendment of Appendix D "Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law" to implement the new reporting process regarding potential Hy's law.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported