EU Clinical Trials Register

Clinical trial results:
A Phase 2a, Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Zunsemetinib vs Placebo in Patients with Moderate-to-Severe Active Psoriatic Arthritis

Summary

EudraCT number	2022-000847-62
Trial protocol	PL
Global end of trial date	03 January 2024

Results information

Result version number	v1 (current)
This version publication date	04 January 2025
First version publication date	04 January 2025

Trial information

Trial identification

Sponsor protocol code	ATI-450-PsA-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05511519
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 139858

Notes:

Sponsors

Sponsor organisation name	Aclaris Therapeutics, Inc.
Sponsor organisation address	701 Lee Rd, Suite 103, Wayne, United States, PA 19087
Public contact	Clinical Operations, Aclaris Therapeutics, Inc., +1 (484) 324-7933, clinicaloperations@aclaristx.com
Scientific contact	Clinical Operations, Aclaris Therapeutics, Inc., +1 (484) 324-7933, clinicaloperations@aclaristx.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	20 March 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 January 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of zunsemetinib in participants with moderate-to-severe psoriatic arthritis (PsA) as measured by 20% improvement in American College of Rheumatology response criteria (ACR20).

Protection of trial subjects:

This study was conducted in accordance with the International Council for Harmonisation tripartite guideline on the ethical principles of Good Clinical Practice (International Council for Harmonisation [ICH] E6), and applicable regulatory requirements including the archiving of essential documents, as well as the ethical principles of the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 July 2022
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	United States: 8
Country: Number of subjects enrolled	Poland: 39
Worldwide total number of subjects	47
EEA total number of subjects	39

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)	40
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 47 participants were randomized and treated in the study. The study was terminated before enrolling the appropriately powered sample size.

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	Placebo BID

Arm description:

Participants received zunsemetinib matched placebo twice daily (BID) orally for 12 weeks.

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

Dosage and administration details:

Placebo matched to zunsemetinib was administered per schedule specified in the arm description.

Arm title	Zunsemetinib 50 mg BID

Arm description:

Participants received zunsemetinib 50 milligrams (mg) BID orally for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Zunsemetinib
Investigational medicinal product code	ATI-450
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Zunsemetinib was administered per dose and schedule specified in the arm description.

Number of subjects in period 1	Placebo BID	Zunsemetinib 50 mg BID
Started	24	23
Received at Least 1 Dose of Study Drug	24	23
Per-protocol (PP) Population	16	17

Completed	16	17
Not completed	8	6
Consent withdrawn by subject	2	1
Investigator's Decision	2	-
Adverse event, non-fatal	1	5
Study Terminated by Sponsor	3	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo BID
Reporting group description:	
Participants received zunsemetinib matched placebo twice daily (BID) orally for 12 weeks.	
Reporting group title	Zunsemetinib 50 mg BID
Reporting group description:	
Participants received zunsemetinib 50 milligrams (mg) BID orally for 12 weeks.	

Reporting group values	Placebo BID	Zunsemetinib 50 mg BID	Total
Number of subjects	24	23	47
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	52.3	46.5	
standard deviation	± 12.30	± 12.10	-
Gender categorical			
Units: Subjects			
Female	14	10	24
Male	10	13	23
Race			
Units: Subjects			
White	24	23	47
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	4	4
Not Hispanic or Latino	24	19	43

End points

End points reporting groups

Reporting group title	Placebo BID
Reporting group description:	
Participants received zunsemetinib matched placebo twice daily (BID) orally for 12 weeks.	
Reporting group title	Zunsemetinib 50 mg BID
Reporting group description:	
Participants received zunsemetinib 50 milligrams (mg) BID orally for 12 weeks.	

Primary: Percentage of Participants Achieving 20% Improvement in American College of Rheumatology Response Criteria (ACR20) at Week 12

End point title	Percentage of Participants Achieving 20% Improvement in American College of Rheumatology Response Criteria (ACR20) at Week 12[1]

End point description:

A participant had an ACR20 response if there was at least a 20% improvement, that is, reduction from Baseline, in tender joint count (TJC) (66/68 joint counts) and swollen joint count (SJC) (28 assessed joints) and in at least 3 of the following 5 parameters: 1) Physician's Global Assessment of Disease Activity (visual analog scale [VAS]: 0=no disease activity to 100=maximum disease activity); 2) Patient's Global Assessment of Disease Activity (VAS: 0=no disease activity to 100=maximum disease activity); 3) Patient's Assessment of Arthritis Pain (VAS: 0=no pain to 100=unbearable pain); 4) Health Assessment Questionnaire - Disability Index (HAQ-DI) (20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, 0=without difficulty to 3=unable to do) and 5) an acute-phase reactant as measured by high sensitivity C-reactive protein (hs-CRP). Intent-to-treat (ITT) population included all randomized participants.

End point type	Primary

End point timeframe:

Week 12

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Study was terminated before enrolling the appropriately powered sample size; hence, no inferential statistics have been reported for the endpoint.

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	23		
Units: percentage of participants				
number (confidence interval 95%)	37.5 (18.1 to 56.9)	39.1 (19.2 to 59.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving 50% Improvement in American College of Rheumatology Response Criteria (ACR50) at Week 12

End point title	Percentage of Participants Achieving 50% Improvement in American College of Rheumatology Response Criteria (ACR50)

	at Week 12

End point description:

A participant had an ACR50 response if there was at least a 50% improvement, that is, reduction from Baseline, in TJC (66/68 joint counts) and SJC (28 assessed joints) and in at least 3 of the following 5 parameters: 1) Physician's Global Assessment of Disease Activity (VAS: 0=no disease activity to 100=maximum disease activity); 2) Patient's Global Assessment of Disease Activity (VAS: 0=no disease activity to 100=maximum disease activity); 3) Patient's Assessment of Arthritis Pain (VAS: 0=no pain to 100=unbearable pain); 4) HAQ-DI (20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, 0=without difficulty to 3=unable to do) and 5) an acute-phase reactant as measured by hs-CRP. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: percentage of participants				
number (confidence interval 95%)	12.5 (0.0 to 28.7)	29.4 (7.8 to 51.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving 70% Improvement in American College of Rheumatology Response Criteria (ACR70) at Week 12

End point title	Percentage of Participants Achieving 70% Improvement in American College of Rheumatology Response Criteria (ACR70) at Week 12

End point description:

A participant had an ACR70 response if there was at least a 70% improvement, that is, reduction from Baseline, in TJC (66/68 joint counts) and SJC (28 assessed joints) and in at least 3 of the following 5 parameters: 1) Physician's Global Assessment of Disease Activity (VAS: 0=no disease activity to 100=maximum disease activity); 2) Patient's Global Assessment of Disease Activity (VAS: 0=no disease activity to 100=maximum disease activity); 3) Patient's Assessment of Arthritis Pain (VAS: 0=no pain to 100=unbearable pain); 4) HAQ-DI (20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, 0=without difficulty to 3=unable to do) and 5) an acute-phase reactant as measured by hs-CRP. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: percentage of participants				
number (confidence interval 95%)	0 (0.0 to 0.0)	11.8 (0.0 to 27.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving ACR20 at Weeks 2, 4, and 8

End point title	Percentage of Participants Achieving ACR20 at Weeks 2, 4, and 8

End point description:

A participant had an ACR20 response if there was at least a 20% improvement, that is, reduction from Baseline, in TJC (66/68 joint counts) and SJC (28 assessed joints) and in at least 3 of the following 5 parameters: 1) Physician's Global Assessment of Disease Activity (VAS: 0=no disease activity to 100=maximum disease activity); 2) Patient's Global Assessment of Disease Activity (VAS: 0=no disease activity to 100=maximum disease activity); 3) Patient's Assessment of Arthritis Pain (VAS: 0=no pain to 100=unbearable pain); 4) HAQ-DI (20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, 0=without difficulty to 3=unable to do) and 5) an acute-phase reactant as measured by hs-CRP. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary

End point timeframe:

Weeks 2, 4, and 8

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: percentage of participants				
number (confidence interval 95%)				
Week 2	6.3 (0.0 to 18.1)	23.5 (3.4 to 43.7)		
Week 4	25.0 (3.8 to 46.2)	47.1 (23.3 to 70.8)		
Week 8	31.3 (8.5 to 54.0)	70.6 (48.9 to 92.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving ACR50 at Weeks 2, 4, and 8

End point title	Percentage of Participants Achieving ACR50 at Weeks 2, 4, and 8

End point description:

A participant had an ACR50 response if there was at least a 50% improvement, that is, reduction from Baseline, in TJC (66/68 joint counts) and SJC (28 assessed joints) and in at least 3 of the following 5 parameters: 1) Physician's Global Assessment of Disease Activity (VAS: 0=no disease activity to 100=maximum disease activity); 2) Patient's Global Assessment of Disease Activity (VAS: 0=no disease activity to 100=maximum disease activity); 3) Patient's Assessment of Arthritis Pain (VAS: 0=no pain to 100=unbearable pain); 4) HAQ-DI (20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, 0=without difficulty to 3=unable to do) and 5) an acute-phase reactant as measured by hs-CRP. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary

End point timeframe:

Weeks 2, 4, and 8

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: percentage of participants				
number (confidence interval 95%)				
Week 2	6.3 (0.0 to 18.1)	5.9 (0.0 to 17.1)		
Week 4	12.5 (0.0 to 28.7)	17.6 (0.0 to 35.8)		
Week 8	12.5 (0.0 to 28.7)	47.1 (23.3 to 70.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving ACR70 at Weeks 2, 4, and 8

End point title	Percentage of Participants Achieving ACR70 at Weeks 2, 4, and 8

End point description:

A participant had an ACR70 response if there was at least a 70% improvement, that is, reduction from Baseline, in TJC (66/68 joint counts) and SJC (28 assessed joints) and in at least 3 of the following 5 parameters: 1) Physician's Global Assessment of Disease Activity (VAS: 0=no disease activity to 100=maximum disease activity); 2) Patient's Global Assessment of Disease Activity (VAS: 0=no disease activity to 100=maximum disease activity); 3) Patient's Assessment of Arthritis Pain (VAS: 0=no pain to 100=unbearable pain); 4) HAQ-DI (20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, 0=without difficulty to 3=unable to do) and 5) an acute-phase reactant as measured by hs-CRP. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary

End point timeframe:

Weeks 2, 4, and 8

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: percentage of participants				
number (confidence interval 95%)				
Week 2	0 (0.0 to 0.0)	0 (0.0 to 0.0)		
Week 4	0 (0.0 to 0.0)	11.8 (0.0 to 27.1)		
Week 8	0 (0.0 to 0.0)	5.9 (0.0 to 17.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in TJC 68 at Week 12

End point title	Change From Baseline in TJC 68 at Week 12

End point description:

An assessment of 68 joints (TJC68) was done for tenderness by pressure manipulation on physical examination. Joint pain/tenderness was classified as either present ("1"), absent ("0"), replaced ("9"), or no assessment ("NA"). The total number of tender joints was calculated by adding all the joints and ranged from 0 to 68, where higher values represented more tender joints. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: tender joints				
arithmetic mean (standard deviation)	-4.9 (± 14.05)	-6.2 (± 4.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in SJC 66 at Week 12

End point title	Change From Baseline in SJC 66 at Week 12

End point description:

An assessment of 66 joints (SJC66) was done for swelling by physical examination. The joints examined for swelling were the same as those examined for tenderness, except the hip joints excluded. Joint swelling was classified as either present ("1"), absent ("0"), replaced ("9") or no assessment ("NA"). The total number of swollen joints was calculated by adding all the joints and ranged from 0 to 66, where higher values represented more swollen joints. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: swollen joint				
arithmetic mean (standard deviation)	-4.9 (± 3.50)	-4.6 (± 3.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HAQ-DI at Week 12

End point title	Change From Baseline in HAQ-DI at Week 12

End point description:

The HAQ-DI is a standardized measure of physical function in arthritis. The HAQ-DI questionnaire contains 20 items divided into 8 domains that measure: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Each item was scored from 0 (no difficulty) to 3 (unable to do) with higher scores being worse. The highest score per domain served as the score for that domain. Domain scores were then averaged for a total HAQ-DI score ranging from 0 (no disability) to 3 (completely disabled); where lower score indicated better outcome. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.3750 (± 0.36799)	-0.3162 (± 0.37007)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient's Global Assessment of Disease Activity (PtGA) at Week 12

End point title	Change From Baseline in Patient's Global Assessment of Disease Activity (PtGA) at Week 12

End point description:

PtGA was evaluated on a 0 millimeters (mm) to 100 mm horizontal VAS with a question referring to psoriatic arthritis disease activity over the past week; 'considering all the ways that your arthritis and psoriasis affects you, rate how you are doing?' The VAS was anchored by the opposite adjectives of "excellent (no disease activity)" (0 mm) and "poor (maximum disease activity)" (100 mm). Lower scores indicated better outcome. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: mm				
arithmetic mean (standard deviation)	-18.5 (± 18.83)	-24.0 (± 28.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Physician's Global Assessment of Disease Activity (PhGA) at Week 12

End point title	Change From Baseline in Physician's Global Assessment of Disease Activity (PhGA) at Week 12

End point description:

PhGA was evaluated on a 0 mm to 100 mm horizontal VAS with a question referring to participant's current psoriatic arthritis disease activity. The VAS was anchored by the opposite adjectives of "very good (no disease activity)" (0 mm) and "very poor (maximum disease activity)" (100 mm). Lower scores indicated better outcome. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: mm				
arithmetic mean (standard deviation)	-19.8 (± 19.98)	-30.1 (± 28.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patients Pain VAS Assessment Score at Week 12

End point title	Change From Baseline in Patients Pain VAS Assessment Score at Week 12

End point description:

Pain was recorded by VAS (0-100 mm) as part of full HAQ-DI questionnaire with 0 mm being 'no pain' and 100 mm being 'severe pain.' Lower scores indicated better outcome. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: mm				
arithmetic mean (standard deviation)	-15.1 (± 27.20)	-21.1 (± 30.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in hs-CRP at Week 12

End point title	Change From Baseline in hs-CRP at Week 12

End point description:

PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: milligrams (mg)/liter (L)				
median (full range (min-max))	-0.45 (-125.80 to 64.80)	-3.80 (-302.90 to 288.60)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Leeds Enthesitis Index (LEI) Score at Week 12

End point title	Change From Baseline in Leeds Enthesitis Index (LEI) Score at Week 12

End point description:

The LEI is used to assess enthesitis in participants with PsA. Entheseal sites included the bilateral lateral epicondyles, medial femoral condyles, and Achilles tendon insertions. Tenderness on examination was recorded as either present (1) or absent (0) for the right and left for each of the 3 sites. The index was the sum for each side of the 3 sites, for an overall score range of 0 to 6. Lower scores indicated better outcome. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.4 (± 1.21)	-1.1 (± 1.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Leeds Dactylitis Index (LDI) Score at Week 12

End point title	Change From Baseline in Leeds Dactylitis Index (LDI) Score at Week 12

End point description:

The circumference of affected and contralateral fingers, and tenderness of affected fingers were assessed by a dactylometer. Ratio of circumference between an affected finger and contralateral unaffected finger was recorded. If both sides were affected, the circumference of affected finger was compared with normative data supplied in a table. Tenderness score (0 [not tender] to 3 [tender]) for a finger with dactylitis was recorded, and a total score was generated for each finger by multiplying the ratio of involved and contralateral digit minus 1 by tenderness score. If multiple fingers were affected, each score was added together to produce a total. A difference in digital circumference of 10% was used to define a finger with dactylitis. If there was no dactylitis, LDI was considered 0. Lower score indicated better outcome. PP population. Number analyzed= participants with dactylitis present at baseline. 99999= Due to single participant, SD could not be calculated.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	7		
Units: units on a scale				
arithmetic mean (standard deviation)	-280.0 (± 99999)	-23.9 (± 44.66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving at Least a 30% Reduction and at Least 1 Unit Reduction From Baseline in the Numerical Rating Scale (NRS30) in Participant's Daily Assessment of Skin Pain at Week 12 Among Participants With Baseline NRS ≥3

End point title	Percentage of Participants Achieving at Least a 30% Reduction and at Least 1 Unit Reduction From Baseline in the Numerical Rating Scale (NRS30) in Participant's Daily Assessment of Skin Pain at Week 12 Among Participants With Baseline NRS ≥3

End point description:

The severity of the participant's pain was assessed by completion of a NRS with 0 indicating no pain and 10 indicating the worst pain imaginable in a 24-hour recall period (maximal daily pain). Participants were instructed to complete the assessment prior to the morning dose of study drug. Percentage of participants achieving at least a 30% reduction and at least 1 unit reduction from Baseline in the NRS in participant's daily assessment of skin pain at Week 12 among participants with Baseline NRS ≥3 were reported. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data. Number analyzed = participants with Baseline NRS ≥3.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	13		
Units: percentage of participants				
number (confidence interval 95%)	28.6 (4.9 to 52.2)	46.2 (19.1 to 73.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving a Static Investigator Global Assessment (sIGA) of Psoriasis of 0 or 1 and at Least a 2-point Improvement From Baseline at Week 12 Among Those With a Baseline Investigator's Global Assessment of at Least 3

End point title	Percentage of Participants Achieving a Static Investigator Global Assessment (sIGA) of Psoriasis of 0 or 1 and at Least a 2-point Improvement From Baseline at Week 12 Among Those With a Baseline Investigator's Global Assessment of at Least 3

End point description:

The sIGA is a 5-point score ranging from 0 (clear) to 4 (severe), based on the investigator's assessment of the average elevation, erythema, and scaling of all psoriatic lesions. The assessment was considered "static" which refers to the participant's disease state at the time of the assessments, without comparison to any of the participant's previous disease states, whether at baseline, or at a previous visit. Percentage of participants achieving a sIGA of psoriasis of 0 or 1 and at least a 2-point improvement from Baseline at Week 12 among those with a Baseline investigator's global assessment of at least 3 were reported. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data. Number analyzed = participants with a Baseline investigator's global assessment of at least 3.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	7		
Units: percentage of participants				
number (confidence interval 95%)	0 (0.0 to 0.0)	0 (0.0 to 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Minimal Disease Activity (MDA) at Week 12

End point title	Percentage of Participants Achieving Minimal Disease Activity (MDA) at Week 12

End point description:

The MDA is a "state" of disease activity in PsA. MDA was considered achieved if at least 5 of the following 7 criteria are met: TJC68 ≤1; SJC66 ≤1; PASI ≤1 or BSA ≤3%; participant pain VAS ≤ 15 (collected as part of the HAQ-DI assessment); PtGA VAS ≤ 20; HAQ-DI≤ 0.5; tender entheseal points or LEI ≤1. Of note, MDA did not include acute-phase reactants, and spondylitis activity. Percentage of participants achieving MDA at Week 12 were reported. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: percentage of participants				
number (confidence interval 95%)	18.8 (0.0 to 37.9)	35.3 (12.6 to 58.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Disease Activity Score Using 28 Joint Count C-reactive Protein (DAS28CRP) at Week 12

End point title	Change From Baseline in Disease Activity Score Using 28 Joint Count C-reactive Protein (DAS28CRP) at Week 12

End point description:

The following equation was used to calculate the DAS28CRP: $DAS28CRP = 0.56\sqrt{TJC28} + 0.28\sqrt{SJC28} + 0.36\ln(CRP + 1) + 0.014 \times (PtGA) + 0.96$.
Interpretation of the DAS28CRP disease activity measure was on a scale of 0 to 9.4, where < 2.6 was considered remission, ≥ 2.6 to < 3.2 was considered low/minimal disease activity, ≥ 3.2 to ≤ 5.1 was considered moderate disease activity, and > 5.1 was considered high/severe disease activity. Lower scores indicated better outcome. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: units on a scale				
arithmetic mean (standard deviation)	-1.1676 (± 1.11594)	-1.3462 (± 0.98930)		

Statistical analyses

No statistical analyses for this end point

Secondary: Psoriasis Area Severity Index (PASI) 50 Response (for Participants With ≥3% Body Surface Area [BSA] Psoriasis [BSA-Ps] at Baseline) at Week 12

End point title	Psoriasis Area Severity Index (PASI) 50 Response (for Participants With ≥3% Body Surface Area [BSA] Psoriasis [BSA-Ps] at Baseline) at Week 12

End point description:

PASI is a measure of psoriatic disease severity. PASI scores range from 0 (no disease symptoms) to 72 (worst disease symptoms), with higher scores reflecting greater disease severity. Total qualitative score (sum of erythema, thickness, and scaling scores; each scored on a scale of 0 [none] to 4 [very severe]) was multiplied by degree of involvement for each anatomic region (BSA-Ps) (each anatomic region [head, trunk, upper limbs, and lower limbs] scored on a scale of 0 [no involvement] to 6 [90% to 100% involvement]) and then multiplied by a constant (0.1 for head, 0.2 for upper limbs, 0.3 for trunk, and 0.4 for lower limbs). Scores for each anatomic region were summed to yield the final PASI. PASI 50 response was evaluated for participants with ≥3% BSA-Ps at baseline and was met when participants achieved > 50% improvement from baseline to post-baseline study visit. PP population as defined in the previous endpoint. Number analyzed = participants with ≥3% BSA-Ps at baseline.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	14		
Units: percentage of participants				
number (confidence interval 95%)	8.3 (0.0 to 24.0)	14.3 (0.0 to 32.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: PASI 75 Response (for Participants With ≥3% BSA-Ps at Baseline) at Week 12

End point title	PASI 75 Response (for Participants With ≥3% BSA-Ps at Baseline) at Week 12

End point description:

PASI is a measure of psoriatic disease severity. PASI scores range from 0 (no disease symptoms) to 72 (worst disease symptoms), with higher scores reflecting greater disease severity. Total qualitative score (sum of erythema, thickness, and scaling scores; each scored on a scale of 0 [none] to 4 [very severe]) was multiplied by degree of involvement for each anatomic region (BSA-Ps) (each anatomic region [head, trunk, upper limbs, and lower limbs] scored on a scale of 0 [no involvement] to 6 [90% to 100% involvement]) and then multiplied by a constant (0.1 for head, 0.2 for upper limbs, 0.3 for trunk, and 0.4 for lower limbs). Scores for each anatomic region were summed to yield the final PASI. PASI 75 response was evaluated for participants with ≥3% BSA-Ps at baseline and was met when participants achieved > 75% improvement from baseline to post-baseline study visit. PP population as defined in the previous endpoint. Number analyzed = participants with ≥3% BSA-Ps at baseline.

End point type	Secondary
End point timeframe:	
Week 12	

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	14		
Units: percentage of participants				
number (confidence interval 95%)	0 (0.0 to 0.0)	7.1 (0.0 to 20.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: PASI 90 Response (for Participants With ≥3% BSA-Ps at Baseline) at Week 12

End point title	PASI 90 Response (for Participants With ≥3% BSA-Ps at Baseline) at Week 12

End point description:

PASI is a measure of psoriatic disease severity. PASI scores range from 0 (no disease symptoms) to 72 (worst disease symptoms), with higher scores reflecting greater disease severity. Total qualitative score (sum of erythema, thickness, and scaling scores; each scored on a scale of 0 [none] to 4 [very severe]) was multiplied by degree of involvement for each anatomic region (BSA-Ps) (each anatomic region [head, trunk, upper limbs, and lower limbs] scored on a scale of 0 [no involvement] to 6 [90% to 100% involvement]) and then multiplied by a constant (0.1 for head, 0.2 for upper limbs, 0.3 for trunk, and 0.4 for lower limbs). Scores for each anatomic region were summed to yield the final PASI. PASI 90 response was evaluated for participants with ≥3% BSA-Ps at baseline and was met when participants achieved > 90% improvement from baseline to post-baseline study visit. PP population as defined in the previous endpoint. Number analyzed = participants with ≥3% BSA-Ps at baseline.

End point type	Secondary
End point timeframe:	
Week 12	

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	14		
Units: percentage of participants				
number (confidence interval 95%)	0 (0.0 to 0.0)	0 (0.0 to 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in PASI Score at Week 12

End point title	Mean Change From Baseline in PASI Score at Week 12

End point description:

PASI is a measure of psoriatic disease severity. PASI scores range from 0 (no disease symptoms) to 72 (worst disease symptoms), with higher scores reflecting greater disease severity. Total qualitative score (sum of erythema, thickness, and scaling scores; each scored on a scale of 0 [none] to 4 [very severe]) was multiplied by degree of involvement for each anatomic region (BSA-Ps) (each anatomic region [head, trunk, upper limbs, and lower limbs] scored on a scale of 0 [no involvement] to 6 [90% to 100% involvement]) and then multiplied by a constant (0.1 for head, 0.2 for upper limbs, 0.3 for trunk, and 0.4 for lower limbs). Scores for each anatomic region were summed to yield the final PASI. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: units on a scale				
arithmetic mean (standard deviation)	-1.48 (± 2.801)	-0.94 (± 3.606)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) Questionnaire Score at Week 12

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) Questionnaire Score at Week 12

End point description:

The FACIT measurement system was originally developed to assess health-related quality-of-life in participants with chronic illnesses. The additional questions of the FACIT-F survey were compiled to

assess anemia-related fatigue. Answers are based on a 5-point Likert scale from 0 ("not at all") to 4 ("very much"). If fewer than seven questions are answered the total score is declared missing. Otherwise, after each item score is subtracted from 4 (except "I have energy" and "I am able to do my usual activities"), the sum of scores is multiplied by 13 and divided by the number of items answered, to produce a total score with range 0 (worst fatigue condition) to 52 (complete functionality) Higher scores indicated less fatigue. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary
End point timeframe:	

Baseline, Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: units on a scale				
arithmetic mean (standard deviation)	6.3 (± 6.94)	2.7 (± 7.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire Score at Week 12

End point title	Change From Baseline in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire Score at Week 12

End point description:

The SAPS is an 11-item questionnaire that includes questions on: pain, itching, redness, scaling, flaking, bleeding, burning, stinging, tenderness, pain due to skin cracking, and joint pain. Each item was scored on a scale of 0 – 10, with 0 being 'No (sign/symptom)' and 10 being 'Worst possible (sign/symptom).' The total score was calculated by summing the individual items. Total scores range from 0 (no disease) to 110 (worst disease conditions), where lower scores indicated better outcome. PP population included all randomized participants who remained on the study drug, completed their assessments for their Day 85 visit, and did not have a major protocol deviation that affected the interpretation of the data.

End point type	Secondary
End point timeframe:	

Baseline, Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: units on a scale				
arithmetic mean (standard deviation)	-13.3 (± 24.02)	-14.5 (± 21.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point description:

TEAEs were defined as adverse events (AEs) with an onset date on or after the date of first administration of study drug and before the date of last administration of study drug + 30 days. An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. A summary of other non-serious AEs and all SAEs, regardless of causality is located in the 'Reported AE section'. Safety Population included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From first dose of study drug up to Week 16

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	23		
Units: participants				
Any TEAEs	5	17		
SAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Zunsemetinib Concentrations

End point title	Zunsemetinib Concentrations

End point description:

Pharmacokinetic (PK) Population included all randomized participants who received at least 1 dose of study drug and had at least 1 evaluable PK assay. 'Number analyzed' = participants evaluable for this endpoint. 'n' = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Predose at Days 1, 8, 15, 29, 43, 57, and 85, and 2-hour postdose at Days 1, 8, and 85

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: nanograms (ng)/mL				
arithmetic mean (standard deviation)				
Predose Day 1 (n=23,23)	2.500 (± 0.0000)	6.913 (± 21.1642)		
2 hr Postdose Day 1 (n=22,22)	2.500 (± 0.0000)	171.268 (± 96.5810)		
Predose Day 8 (n=23,19)	2.500 (± 0.0000)	111.763 (± 68.5513)		
2 hr Postdose Day 8 (n=23,19)	2.500 (± 0.0000)	267.242 (± 91.4422)		
Predose Day 15 (n=23,20)	2.500 (± 0.0000)	116.610 (± 67.9135)		
Predose Day 29 (n=22,17)	2.500 (± 0.0000)	77.435 (± 42.4650)		
Predose Day 43 (n=19,16)	2.500 (± 0.0000)	87.556 (± 51.0368)		
Predose Day 57 (n=18,17)	2.500 (± 0.0000)	106.688 (± 57.6147)		
Predose Day 85 (n=17,16)	2.500 (± 0.0000)	76.369 (± 47.4475)		
2 hr Postdose Day 85 (n=15,15)	2.500 (± 0.0000)	228.627 (± 110.0968)		

Statistical analyses

No statistical analyses for this end point

Secondary: Metabolite (CDD-2164) Concentrations

End point title	Metabolite (CDD-2164) Concentrations
End point description:	

PK Population included all randomized participants who received at least 1 dose of study drug and had at least 1 evaluable PK assay. 'Number analyzed' = participants evaluable for this endpoint. 'n' = participants evaluable at specified timepoint.

End point type	Secondary
End point timeframe:	

Predose at Days 1, 8, 15, 29, 43, 57, and 85, and 2-hour postdose at Days 1, 8, and 85

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: ng/mL				
arithmetic mean (standard deviation)				
Predose Day 1 (n=23,23)	0.250 (± 0.0000)	0.965 (± 3.4301)		
2 hr Postdose Day 1 (n=22,22)	0.274 (± 0.1124)	54.365 (± 35.0266)		
Predose Day 8 (n=23,19)	0.250 (± 0.0000)	26.725 (± 15.6869)		
2 hr Postdose Day 8 (n=23,19)	0.250 (± 0.0000)	86.237 (± 38.8906)		
Predose Day 15 (n=23,20)	0.250 (± 0.0000)	30.975 (± 27.5939)		
Predose Day 29 (n=22,17)	0.250 (± 0.0000)	16.472 (± 8.7831)		
Predose Day 43 (n=19,16)	0.250 (± 0.0000)	18.127 (± 10.8765)		
Predose Day 57 (n=18,17)	0.250 (± 0.0000)	22.997 (± 13.5215)		
Predose Day 85 (n=17,16)	0.250 (± 0.0000)	17.210 (± 11.2947)		
2 hr Postdose Day 85 (n=15,15)	0.250 (± 0.0000)	70.853 (± 40.8293)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short-Form (SF)-36 Physical Component Summary (PCS) Score at Week 12

End point title	Change From Baseline in Short-Form (SF)-36 Physical Component Summary (PCS) Score at Week 12

End point description:

SF-36 is a generic measure to assess general health and well-being (that is, health-related quality-of life). The short version 2 (SF-36v2) consists of 36 questions were to be used: 22 make up the PCS and the remaining 14 make the mental health component summary (MCS). For the SF-36v2, the analyses specifically focuses on the PCS which is composed of 4 scales assessing physical function, role limitations caused by physical problems, bodily pain, and general health. Higher scores represent better physical health. As specified in Statistical Analysis Plan (SAP), due to early termination of study, SF-36 PCS scores were not derived or summarized.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo BID	Zunsemetinib 50 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: units on a scale				
arithmetic mean (standard deviation)	( )	( )		

Notes:

[2] - Due to early termination of study, SF-36 PCS scores were not derived or summarized.

[3] - Due to early termination of study, SF-36 PCS scores were not derived or summarized.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to Week 16

Adverse event reporting additional description:

Safety Population included all randomized participants who received at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Placebo BID

Reporting group description:

Participants received zunsemetinib matched placebo BID orally for 12 weeks.

Reporting group title	Zunsemetinib 50 mg BID

Reporting group description:

Participants received zunsemetinib 50 mg BID orally for 12 weeks.

Serious adverse events	Placebo BID	Zunsemetinib 50 mg BID	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Placebo BID	Zunsemetinib 50 mg BID	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	11 / 23 (47.83%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 24 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Nervous system disorders			
Dizziness			

subjects affected / exposed	0 / 24 (0.00%)	6 / 23 (26.09%)	
occurrences (all)	0	6	
Tremor			
subjects affected / exposed	0 / 24 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	0 / 24 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2022	- Updated allowed prior medications in inclusion criteria. - Clarified meaning of end of study in context of prohibited medications during the study.
14 December 2022	- EudraCT number added. - Footnote of 'Schedule of Assessments Table' modified to add acceptable window for PK blood sampling. - Inclusion criteria modified to broaden participant population to facilitate recruitment. - Exclusion criteria modified to broaden and streamline enrolled participant population to facilitate recruitment. - Updated allowed list of medications during the study. - Day 1 time point removed for proportion of participants with ACR 20/50/70. - Updated version of self-assessment of psoriasis symptoms scale.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated before enrolling the appropriately powered sample size. No inferential statistics have been calculated for this study and only descriptive statistics are provided. Furthermore, SF-36 PCS scores were not derived or summarized.

Notes: