Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Evaluate the Efficacy and Safety of RIST4721 in Subjects with Palmoplantar Pustulosis

Summary

EudraCT number	2018-004176-35
Trial protocol	DE
Global end of trial date	19 November 2019

Results information

Result version number	v1 (current)
This version publication date	30 November 2020
First version publication date	30 November 2020

Trial information

Trial identification

Sponsor protocol code	RIST4721-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03988335
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aristea Therapeutics, Inc.
Sponsor organisation address	12770 High Bluff Drive, Suite #380, San Diego, United States, 92130
Public contact	Aristea Therapeutics, Aristea Therapeutics, info@aristeatx.com
Scientific contact	Aristea Therapeutics, Aristea Therapeutics, info@aristeatx.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	19 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 November 2019
Global end of trial reached?	Yes
Global end of trial date	19 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the efficacy of RIST4721 versus placebo in adult subjects with moderate to severe palmoplantar pustulosis (PPP) using a range of efficacy endpoints

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 Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 February 2019
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	Germany: 12
Country: Number of subjects enrolled	Canada: 23
Worldwide total number of subjects	35
EEA total number of subjects	12

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)	34
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects must have at least a 6-month history of PPP and have moderate or severe PPP.

Period 1

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

Blinding implementation details:

This study was double blind. In order to reduce risk of breaking the blind, investigators, the study staff, the CRO, and the sponsor’s study team did not receive absolute and relative neutrophil and WBC count results, starting on Day 7. A medical monitor reviewed the blinded data and ensured that the safety of all enrolled subjects was preserved.

Arms

Are arms mutually exclusive?	Yes
Arm title	RIST4721 300 mg

Arm description:

This arm was randomized to receive 300 mg of RIST4721 once daily for 28 days.

Arm type	Experimental
Investigational medicinal product name	RIST4721
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

RIST4721 300 mg oral solution was to be taken once daily for 28 days.

Arm title	Placebo

Arm description:

This arm was randomized to receive placebo once daily for 28 days.

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

Dosage and administration details:

Placebo oral solution was to be taken once daily for 28 days.

Number of subjects in period 1	RIST4721 300 mg	Placebo
Started	16	19
Completed	14	18
Not completed	2	1
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	RIST4721 300 mg
Reporting group description:	
This arm was randomized to receive 300 mg of RIST4721 once daily for 28 days.	
Reporting group title	Placebo
Reporting group description:	
This arm was randomized to receive placebo once daily for 28 days.	

Reporting group values	RIST4721 300 mg	Placebo	Total
Number of subjects	16	19	35
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)	15	19	34
From 65-84 years	1	0	1
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	12	16	28
Male	4	3	7

Subject analysis sets	
Subject analysis set title	RIST4721 300 mg (mITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All subjects who received at least one dose of RIST4721 300 mg.	
Subject analysis set title	Placebo (mITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All subjects who received at least one dose of Placebo.	

Reporting group values	RIST4721 300 mg (mITT)	Placebo (mITT)	
Number of subjects	15	19	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	

Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	19	
From 65-84 years	1	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	12	16	
Male	3	3	

End points

End points reporting groups

Reporting group title	RIST4721 300 mg
Reporting group description:	
This arm was randomized to receive 300 mg of RIST4721 once daily for 28 days.	
Reporting group title	Placebo
Reporting group description:	
This arm was randomized to receive placebo once daily for 28 days.	
Subject analysis set title	RIST4721 300 mg (mITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All subjects who received at least one dose of RIST4721 300 mg.	
Subject analysis set title	Placebo (mITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All subjects who received at least one dose of Placebo.	

Primary: Relative change from baseline in fresh pustule count at Day 28

End point title	Relative change from baseline in fresh pustule count at Day 28
End point description:	
End point type	Primary
End point timeframe:	
Baseline to Day 28	

End point values	RIST4721 300 mg (mITT)	Placebo (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	19		
Units: Relative change				
arithmetic mean (standard deviation)	0.86 (± 0.692)	0.53 (± 0.561)		

Statistical analyses

Statistical analysis title	Hochberg’s method
Comparison groups	Placebo (mITT) v RIST4721 300 mg (mITT)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.24
Method	Hochberg’s method

Notes:

[1] - The primary endpoints were first tested at alpha of 10% (2-sided). If the larger p-value was less than 10% (2sided), both primary endpoints were to be declared statistically significant. If the larger pvalue was greater than 10%, but the smaller p-value was less than 5% (2-sided), then the primary

endpoint with the smaller p-value was to be declared statistically significant.

Primary: Relative change from baseline in total pustule count at Day 28	
End point title	Relative change from baseline in total pustule count at Day 28
End point description:	
End point type	Primary
End point timeframe:	
Baseline to Day 28	

End point values	RIST4721 300 mg (mITT)	Placebo (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	19		
Units: Relative change				
arithmetic mean (standard deviation)	0.99 (± 0.667)	0.96 (± 0.672)		

Statistical analyses

Statistical analysis title	Hochberg’s method

Statistical analysis description:

The primary endpoints were first tested at alpha of 10% (2-sided). If the larger p-value was less than 10% (2sided), both primary endpoints were to be declared statistically significant. If the larger pvalue was greater than 10%, but the smaller p-value was less than 5% (2-sided), then the primary endpoint with the smaller p-value was to be declared statistically significant.

Comparison groups	RIST4721 300 mg (mITT) v Placebo (mITT)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.804
Method	Hochberg’s method.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From ICF signature to end of study participation.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1
Reporting groups	
Reporting group title	RIST4721 300 mg
Reporting group description: All subjects that received at least one dose of RIST4721.	
Reporting group title	Placebo
Reporting group description: All subjects that received at least one dose of Placebo.	

Serious adverse events	RIST4721 300 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 19 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	RIST4721 300 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 15 (86.67%)	7 / 19 (36.84%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 15 (6.67%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 15 (6.67%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 15 (6.67%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Investigations			
Bacterial test			
subjects affected / exposed	1 / 15 (6.67%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Blood glucose increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Blood triglycerides increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	2 / 15 (13.33%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Ligament sprain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Concussion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Headache			

subjects affected / exposed	1 / 15 (6.67%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 15 (13.33%)	0 / 19 (0.00%)	
occurrences (all)	2	0	
Leukopenia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 15 (33.33%)	1 / 19 (5.26%)	
occurrences (all)	6	1	
Abnormal faeces			
subjects affected / exposed	2 / 15 (13.33%)	0 / 19 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	2 / 15 (13.33%)	0 / 19 (0.00%)	
occurrences (all)	2	0	
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Skin fissures			
subjects affected / exposed	1 / 15 (6.67%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Urine odour abnormal			
subjects affected / exposed	3 / 15 (20.00%)	0 / 19 (0.00%)	
occurrences (all)	3	0	
Micturition disorder			
subjects affected / exposed	0 / 15 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness			

subjects affected / exposed	2 / 15 (13.33%)	0 / 19 (0.00%)	
occurrences (all)	2	0	
Pain in extremity			
subjects affected / exposed	1 / 15 (6.67%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Osteoarthritis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Infections and infestations			
Folliculitis			
subjects affected / exposed	2 / 15 (13.33%)	0 / 19 (0.00%)	
occurrences (all)	3	0	
Nasopharyngitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Post procedural cellulitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 15 (6.67%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Increased appetite			
subjects affected / exposed	1 / 15 (6.67%)	0 / 19 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2019	The purpose of this amendment was to revise inclusion and exclusion criteria, to substantiate the potential risks, benefits, and risk-benefit analysis, to provide clarification about optional sub-studies and to specify where the Reference Safety Information could be found. Other minor edits were also made for completeness.
22 March 2019	The purpose of this amendment was to add an exclusion criteria following the update of the IB regarding possible drug-drug interactions and to add a lifestyle consideration regarding consumption of grapefruit-containing products due to possible interactions with CYP3A4. The Physician's Global Assessment Scale was also revised for accuracy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported