Clinical trial results:
Efficacy of oral alitretinoin treatment in patients with palmo-plantar pustulosis (PPP) inadequately responding to standard topical treatment

Summary

EudraCT number	2010-022843-39
Trial protocol	DE GB NL
Global end of trial date	16 April 2014

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	18 December 2014

Trial information

Trial identification

Sponsor protocol code	ATN117221

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01245140
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine the response, based on the palmo-plantar pustulosis psoriasis area and severity index (PPPASI) at the end of treatment (week 24).

Protection of trial subjects:

Not applicable.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 April 2011
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: 3
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 20
Worldwide total number of subjects	33
EEA total number of subjects	33

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)	28
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The total study duration was 33 weeks, with a Screening Period of up to 4 weeks, followed by 24 weeks of treatment and a 5-week safety Follow-up Period. Participants who met eligibility criteria were randomized (2:1) to receive 30 milligrams (mg) alitretinoin or matching placebo, given orally as gelatin capsules, once daily (QD) for up to 24 weeks.

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, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Matching placebo

Arm description:

Participants received matching placebo orally QD for up to 24 weeks.

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

Dosage and administration details:

daily dosing
Formulation:
CAPSULE CONTENT - Soya-bean oil (refined), partially hydrogenated soya-bean oil, triglycerides (medium chain), beeswax (yellow), all-rac-α-tocopherol
CAPSULE SHELL – gelatin, glycerol, sorbitol (liquid [non-crystallising]), water (purified), iron oxide (E 172)

Arm title	Alitretinoin 30 mg

Arm description:

Participants received an alitretinoin 30 milligram (mg) capsule orally QD for up to 24 weeks.

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

Dosage and administration details:

30 milligrams (mg), daily dosing
Formulation:
CAPSULE CONTENT - Soya-bean oil (refined), partially hydrogenated soya-bean oil, triglycerides (medium chain), beeswax (yellow), all-rac-α-tocopherol
CAPSULE SHELL – gelatin, glycerol, sorbitol (liquid [non-crystallising]), water (purified), iron oxide (E 172)

Number of subjects in period 1	Matching placebo	Alitretinoin 30 mg
Started	9	24
Completed	6	14
Not completed	3	10
'Refused Treatment/Did Not Cooperate '	-	1
Adverse event, non-fatal	1	3
Withdrawal by Subject	-	1
Lack of efficacy	2	4
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Matching placebo
Reporting group description:	
Participants received matching placebo orally QD for up to 24 weeks.	
Reporting group title	Alitretinoin 30 mg
Reporting group description:	
Participants received an alitretinoin 30 milligram (mg) capsule orally QD for up to 24 weeks.	

Reporting group values	Matching placebo	Alitretinoin 30 mg	Total
Number of subjects	9	24	33
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	49	48.83	
standard deviation	± 16.32	± 14.94	-
Gender categorical Units: Subjects			
Female	5	14	19
Male	4	10	14
Race, Customized Units: Subjects			
Caucasian/White	8	22	30
Oriental	1	0	1
Black	0	1	1
North African	0	1	1

End points

End points reporting groups

Reporting group title	Matching placebo
Reporting group description:	
Participants received matching placebo orally QD for up to 24 weeks.	
Reporting group title	Alitretinoin 30 mg
Reporting group description:	
Participants received an alitretinoin 30 milligram (mg) capsule orally QD for up to 24 weeks.	

Primary: Change from Baseline in the palmo-plantar pustulosis psoriasis area and severity index (PPPASI) score at the end of treatment (EOT) (Week 24) or at the last assessment

End point title	Change from Baseline in the palmo-plantar pustulosis psoriasis area and severity index (PPPASI) score at the end of treatment (EOT) (Week 24) or at the last assessment

End point description:

The investigator evaluated the PPPASI score on a 5-point scale. The parameters of erythema, total number of pustules, and desquamation were scored for the right/left palm and the right/left sole. After correcting the scores for area (based on a 7-point scale) and the site involved (palm or sole), the PPPASI score per palm/sole was produced. The final PPPASI score was calculated as the sum of the PPPASI score for the right sole + the PPPASI score for the left sole + the PPPASI score for the right palm + the PPPASI score for the left palm and ranges from 0 (no palmo-plantar pustulosis psoriasis [PPP]) to 72 (most severe PPP). Change from Baseline is defined as value at the EOT minus the Baseline value.

End point type	Primary

End point timeframe:

Baseline and EOT (Week 24) or the last assessment

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[1]	22[2]		
Units: scores on a scale				
arithmetic mean (standard deviation)	-44.6 (± 45.9)	-45.2 (± 32.8)		

Notes:

[1] - Full Analysis Set: treated participants with >=1 efficacy result after receiving study medication

[2] - Full Analysis Set: treated participants with >=1 efficacy result after receiving study medication

Statistical analyses

Statistical analysis title	Statistical Analysis for Primary Endpoint #1
Comparison groups	Matching placebo v Alitretinoin 30 mg
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9705
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.5731

Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.9738
upper limit	32.12

Primary: Number of participants with PPPASI 50 response and PPPASI 75 response

End point title	Number of participants with PPPASI 50 response and PPPASI 75 response

End point description:

The investigator evaluated the PPPASI score on a 5-point scale. The parameters of erythema, total number of pustules, and desquamation were scored for the right/left palm and the right/left sole. After correcting the scores for area (based on a 7-point scale) and the site involved (palm or sole), the PPPASI score per palm/sole was produced. The final PPPASI score was calculated as the sum of the PPPASI score for the right sole + the PPPASI score for the left sole + the PPPASI score for the right palm + the PPPASI score for the left palm and ranges from 0 (no palmo-plantar pustulosis psoriasis [PPP]) to 72 (most severe PPP). Change from Baseline is defined as value at the EOT minus the Baseline value. PPPASI 50 response and PPPASI 75 response are defined as a 50% and 75% decrease, respectively, in the PPPASI score from Baseline.

End point type	Primary

End point timeframe:

From Baseline until EOT (Week 24) or the last assessment

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[3]	22[4]		
Units: participants				
PPPASI 50 response	6	11		
PPPASI 75 response	3	5		

Notes:

[3] - Full Analysis Set

[4] - Full Analysis Set

Statistical analyses

Statistical analysis title	PPPASI 50 response
Comparison groups	Matching placebo v Alitretinoin 30 mg
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4564
Method	Fisher exact

Statistical analysis title	PPPASI 75 response
Comparison groups	Matching placebo v Alitretinoin 30 mg

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6595
Method	Fisher exact

Secondary: Total pustule count at Baseline; Weeks 4, 8, 12, 16, and 20; and at EOT (Week 24)

End point title	Total pustule count at Baseline; Weeks 4, 8, 12, 16, and 20; and at EOT (Week 24)

End point description:

The overall number of fresh and older pustules on the left and right palms and soles was assessed at Baseline, at each visit during the treatment period (Weeks 4, 8, 12, 16, and 20), and at the EOT visit. The total pustule count was calculated as the sum of the pustule count for the left/right palm and left/right sole.

End point type	Secondary

End point timeframe:

Baseline; Weeks 4, 8, 12, 16, and 20; and EOT (Week 24)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[5]	22[6]		
Units: Pustule count				
arithmetic mean (standard deviation)				
Baseline, n=9, 22	82.7 (± 59.1)	106 (± 128.2)		
Week 4, n=9, 20	71.6 (± 66.5)	31 (± 43.5)		
Week 8, n=7, 20	69.7 (± 30.8)	30.4 (± 38.6)		
Week 12, n=7, 17	70.4 (± 63.2)	21.5 (± 37.8)		
Week 16, n=6, 16	26.8 (± 25.5)	26 (± 42)		
Week 20, n=6, 14	35.8 (± 37.7)	30.5 (± 51.2)		
End of Treatment, n=8, 20	55.4 (± 104.5)	33.6 (± 49.6)		

Notes:

[5] - Full Analysis Set. Only participants available at the specified time points were analyzed (n=X, X).

[6] - Full Analysis Set. Only participants available at the specified time points were analyzed (n=X, X).

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from Baseline (BL) in total pustule count at Weeks 4, 8, 12, 16, and 20 and at EOT (Week 24)

End point title	Absolute change from Baseline (BL) in total pustule count at Weeks 4, 8, 12, 16, and 20 and at EOT (Week 24)

End point description:

The overall number of fresh and older pustules on the left and right palms and soles was assessed at Baseline, at each visit during the treatment period (Weeks 4, 8, 12, 16, and 20), and at the End of Treatment visit. The total pustule count was calculated as the sum of the pustule count for the left/right palm and left/right sole. Change from Baseline is defined as the value at the post-Baseline visit minus the Baseline value.

End point type	Secondary

End point timeframe:

Baseline; Weeks 4, 8, 12, 16, and 20; and EOT (Week 24)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[7]	22[8]		
Units: Pustule count				
arithmetic mean (standard deviation)				
Week 4, n=9, 20	-11.1 (± 58.4)	-75.3 (± 113.2)		
Week 8, n=7, 20	-7.9 (± 51.5)	-75.9 (± 124.4)		
Week 12, n=7, 17	-7.1 (± 75.5)	-74.2 (± 111.7)		
Week 16, n=6, 16	-55.2 (± 56.5)	-75.6 (± 113)		
Week 20, n=6, 14	-46.2 (± 37.8)	-65.1 (± 106.4)		
End of Treatment, n=8, 20	-31.3 (± 79.4)	-82.1 (± 121.3)		

Notes:

[7] - Full Analysis Set. Only participants available at the specified time points were analyzed (n=X, X).

[8] - Full Analysis Set. Only participants available at the specified time points were analyzed (n=X, X).

Statistical analyses

Statistical analysis title	Change in Total Pustule Count: BL to Last Visit
Comparison groups	Matching placebo v Alitretinoin 30 mg
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51
Method	Wilcoxon test: Exact Test

Secondary: Summary of the Modified Psoriasis Area Severity Index (mPASI) score at Baseline; Weeks 4, 8, 12, 16, and 20; and EOT (Week 24)

End point title	Summary of the Modified Psoriasis Area Severity Index (mPASI) score at Baseline; Weeks 4, 8, 12, 16, and 20; and EOT (Week 24)

End point description:

Psoriatic plaques were graded based on three criteria: redness (R), thickness (T), and scaliness (S). Severity was rated for each criterion on a 5-point scale (0=no involvement, up to 4=severe involvement). The fraction of the total surface area affected on the head, upper extremities, trunk, and lower extremities was graded on a 7-point scale (0=no involvement, up to 6=greater than 90% involvement). The four body regions were weighted to reflect their respective proportion of body surface area, and the composite mPASI score for all body regions was calculated based on the redness, thickness, and scaliness scores of plaques (0-4 each) for the head, upper extremities, trunk, and lower extremities and the area of psoriatic involvement score (0-6). The highest possible mPASI score is 72; the lowest is 0. mPASI scores were continuous, with 0.1 increments within these values.

End point type	Secondary

End point timeframe:

Baseline; Weeks 4, 8, 12, 16, and 20; and EOT (Week 24)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[9]	22[10]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline, n=9, 21	0.2 (± 0.4)	0.5 (± 0.9)		
Week 4, n=9, 20	0.3 (± 0.6)	0.4 (± 0.9)		
Week 8, n=7, 20	0 (± 0.1)	0.4 (± 0.9)		
Week 12, n=7, 17	0 (± 0.1)	0.4 (± 0.9)		
Week 16, n=6, 16	0 (± 0)	0.2 (± 0.5)		
Week 20, n=6, 14	0 (± 0.1)	0.1 (± 0.3)		
End of Treatment, n=8, 20	0.7 (± 1.9)	0.3 (± 0.7)		

Notes:

[9] - Full Analysis Set. Only participants available at the specified time points were analyzed (n=X, X).

[10] - Full Analysis Set. Only participants available at the specified time points were analyzed (n=X, X).

Statistical analyses

Statistical analysis title	Relative change in mPASI score: BL to Last Visit
Comparison groups	Matching placebo v Alitretinoin 30 mg
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Wilcoxon test: Exact Test

Secondary: Change from Baseline in the mPASI score at EOT (Week 24) or at the last assessment

End point title	Change from Baseline in the mPASI score at EOT (Week 24) or at the last assessment

End point description:

Psoriatic plaques were graded based on three criteria: redness (R), thickness (T), and scaliness (S). Severity was rated for each criterion on a 5-point scale (0=no involvement, up to 4=severe involvement). The fraction of the total surface area affected on the head, upper extremities, trunk, and lower extremities was graded on a 7-point scale (0=no involvement, up to 6=greater than 90% involvement). The four body regions were weighted to reflect their respective proportion of body surface area, and the composite mPASI score for all body regions was calculated based on the redness, thickness, and scaliness scores of plaques (0-4 each) for the head, upper extremities, trunk, and lower extremities and the area of psoriatic involvement score (0-6). The highest possible mPASI score is 72; the lowest is 0. mPASI scores were continuous, with 0.1 increments within these values. Change from Baseline is defined as the value at EOT minus the Baseline value.

End point type	Secondary

End point timeframe:

Baseline and EOT (Week 24) or the last assessment

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[11]	22[12]		
Units: scores on a scale				
arithmetic mean (standard deviation)	-95.8 (± 7.2)	-51 (± 38.3)		

Notes:

[11] - Full Analysis Set

[12] - Full Analysis Set

Statistical analyses

Statistical analysis title	Secondary Endpoint
Comparison groups	Matching placebo v Alitretinoin 30 mg
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2358
Method	ANCOVA
Parameter estimate	Least squared estimation
Point estimate	49.4927
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.083
upper limit	148.07

Secondary: Number of participants with mPASI 50 response and mPASI 75 response

End point title	Number of participants with mPASI 50 response and mPASI 75 response

End point description:

Psoriatic plaques were graded based on three criteria: redness (R), thickness (T), and scaliness (S). Severity was rated for each criterion on a 5-point scale (0=no involvement, up to 4=severe involvement). The fraction of the total surface area affected on the head, upper extremities, trunk, and lower extremities was graded on a 7-point scale (0=no involvement, up to 6=greater than 90% involvement). The four body regions were weighted to reflect their respective proportion of body surface area, and the composite mPASI score for all body regions was calculated. mPASI 50 response and mPASI 75 response is defined as a 50% and 75% decrease, respectively, in the mPASI score from Baseline. FAS=Full Analysis Set.

End point type	Secondary

End point timeframe:

From Baseline until EOT (Week 24)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[13]	6[14]		
Units: participants				
mPASI 50 response	3	2		
mPASI 75 response	3	2		

Notes:

[13] - FAS. Participants with lesions in areas of the body other than the hands and feet were assessed.

[14] - FAS. Participants with lesions in areas of the body other than the hands and feet were assessed.

Statistical analyses

Statistical analysis title	mPASI 50 response
Comparison groups	Matching placebo v Alitretinoin 30 mg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1667
Method	Fisher exact

Statistical analysis title	mPASI 75 response
Comparison groups	Matching placebo v Alitretinoin 30 mg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1667
Method	Fisher exact

Secondary: Summary of the Nail Psoriasis Severity Index (NAPSI) score at Baseline, Week 12, and EOT (Week 24)

End point title	Summary of the Nail Psoriasis Severity Index (NAPSI) score at Baseline, Week 12, and EOT (Week 24)

End point description:

The severity of nail lesions was assessed for all participants with psoriatic nail involvement by obtaining the NAPSI score at Baseline, at Week 12, and at the EOT visit. Scores were taken for fingernails only. No scores were taken for participants with traumatic or fungal changes in nails. The nail was divided into quadrants, each of which was rated with a 0 or 1, based on the absence (0) or presence (1) of pathological signs resulting from involvement of both the nail matrix and the nail bed. Each nail was given a score for nail bed psoriasis (0-4) and nail matrix psoriasis (0-4) depending on the presence of nail psoriasis in that quadrant. Possible scores for matrix and nail bed psoriasis: 0=none, 1=present in 1/4 nail, 2=present in 2/4 nail, 3=present in 3/4 nail, 4=present in 4/4 nail. The NAPSI score ranges from 0 to 8 for one nail and from 0 to 80 for 10 nails.

End point type	Secondary

End point timeframe:

Baseline, Week 12, and EOT (Week 24)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[15]	22[16]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
NAPSI-bed, Baseline, n=9, 20	1.1 (± 2.3)	1.2 (± 1.9)		
NAPSI-bed, Week 12, n=7, 17	0.4 (± 1.1)	1.3 (± 3.3)		
NAPSI-bed, End of Treatment, n=8, 19	1.6 (± 2.8)	0.9 (± 2)		
NAPSI-matrix, Baseline, n=9, 20	3.9 (± 6.2)	3.6 (± 6.2)		
NAPSI-matrix, Week 12, n=7, 17	2.1 (± 3.7)	2.6 (± 6)		
NAPSI-matrix, End of Treatment, n=8, 19	4.3 (± 6)	2.6 (± 6)		

Notes:

[15] - Full Analysis Set. Only participants available at the specified time points were analyzed (n=X, X).

[16] - Full Analysis Set. Only participants available at the specified time points were analyzed (n=X, X).

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from Baseline in the NAPSI score at Week 12 and EOT (Week 24)

End point title	Absolute change from Baseline in the NAPSI score at Week 12 and EOT (Week 24)

End point description:

The severity of nail lesions was assessed for all participants with psoriatic nail involvement by obtaining the NAPSI score at Baseline, at Week 12, and at the EOT visit. Scores were taken for fingernails only. No scores were taken for participants with traumatic or fungal changes in nails. The nail was divided into quadrants, each of which was rated with a 0 or 1, based on the absence (0) or presence (1) of pathological signs resulting from involvement of both the nail matrix and the nail bed. Each nail was given a score for nail bed psoriasis (0-4) and nail matrix psoriasis (0-4) depending on the presence of nail psoriasis in that quadrant. Possible scores for matrix and nail bed psoriasis: 0=none, 1=present in 1/4 nail, 2=present in 2/4 nail, 3=present in 3/4 nail, 4=present in 4/4 nail. The NAPSI score ranges from 0 to 8 for one nail and from 0 to 80 for 10 nails. Change from Baseline is defined as the value at the post-Baseline visit minus the Baseline value.

End point type	Secondary

End point timeframe:

Baseline, Week 12, and EOT (Week 24)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[17]	22[18]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
NAPSI-bed, Week 12, n=7, 17	-0.4 (± 1.1)	0.3 (± 2.4)		
NAPSI-bed, End of Treatment, n=8, 18	0.4 (± 2.2)	-0.3 (± 1.6)		
NAPSI-matrix, Week 12, n=7, 17	-1.4 (± 3.8)	-0.5 (± 2)		
NAPSI-matrix, End of Treatment, n=8, 18	0.8 (± 5.5)	-0.1 (± 5)		

Notes:

[17] - Full Analysis Set. Only participants available at the specified time points were analyzed (n=X, X).

[18] - Full Analysis Set. Only participants available at the specified time points were analyzed (n=X, X).

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any AE or SAE and an AE/SAE related to study treatment

End point title	Number of participants with any AE or SAE and an AE/SAE related to study treatment

End point description:

An AE was any adverse change from the participant's Baseline (pre-treatment) clinical condition, including intercurrent illness, which occured during the course of a clinical study after written informed consent had been given, whether considered related to treatment or not. The relationship of AEs to the study treatment was assessed as unrelated, remotely related, possibly related, and probably related. For an AE to be considered serious, it fell into one or more of the following categories: results in death, is life threatening, results in persistent or significant disability/incapacity, results in or prolongs inpatient hospitalization, and is a congenital abnormality or birth defect.

End point type	Secondary

End point timeframe:

From Baseline until safety follow up (Week 29)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[19]	24[20]		
Units: participants				
Any AE	8	18		
Any AE remotely related to study medication	6	15		
Any SAE	0	1		
Any SAE remotely related to study medication	0	1		

Notes:

[19] - Safety Population: all randomized participants who received at least one dose of study medication

[20] - Safety Population: all randomized participants who received at least one dose of study medication

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from Baseline in fasted lipid laboratory test values at Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and at safety follow-up (Week 29)

End point title	Absolute change from Baseline in fasted lipid laboratory test values at Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and at safety follow-up (Week 29)

End point description:

Fasted lipid laboratory parameters included triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol. Change from Baseline is defined as the

value at the post-Baseline visit minus the Baseline value.

End point type	Secondary

End point timeframe:

Baseline; Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and safety follow-up (Week 29)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[21]	24[22]		
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Triglycerides, Week 4, n=9, 19	0.6 (± 2.3)	2.4 (± 3.7)		
Triglycerides, Week 8, n=7, 20	1 (± 1.9)	3.8 (± 5.7)		
Triglycerides, Week 12, n=6, 17	2.5 (± 3.6)	5.8 (± 8.7)		
Triglycerides, Week 16, n=5, 16	2.6 (± 1.7)	4.2 (± 5.2)		
Triglycerides, Week 20, n=6, 14	2.6 (± 4.1)	5.6 (± 6.2)		
Triglycerides, End of Treatment, n=7, 20	-0.7 (± 2.5)	3.3 (± 5.6)		
Triglycerides, safety follow-up, n=9, 21	1.2 (± 3.4)	2.8 (± 5.8)		
Total cholesterol, Week 4, n=9, 19	0 (± 0.5)	0.6 (± 0.6)		
Total cholesterol, Week 8, n=7, 20	-0.2 (± 0.5)	0.7 (± 0.8)		
Total cholesterol, Week 12, n=6, 17	0.1 (± 0.3)	0.7 (± 0.9)		
Total cholesterol, Week 16, n=5, 16	0.1 (± 0.5)	0.6 (± 0.8)		
Total cholesterol, Week 20, n=6, 14	0.1 (± 0.8)	0.7 (± 1.1)		
Total cholesterol, End of Treatment, n=8, 20	-0.1 (± 0.5)	0.7 (± 0.7)		
Total cholesterol, safety follow-up, n=9, 22	0 (± 0.5)	0.3 (± 0.8)		
HDL cholesterol, Week 4, n=8, 19	-0.1 (± 0.2)	-0.1 (± 0.1)		
HDL cholesterol, Week 8, n=7, 20	-0.1 (± 0.2)	-0.2 (± 0.2)		
HDL cholesterol, Week 12, n=6, 17	0 (± 0.2)	-0.2 (± 0.2)		
HDL cholesterol, Week 16, n=5, 16	-0.1 (± 0.1)	-0.2 (± 0.2)		
HDL cholesterol, Week 20, n=6, 14	0 (± 0.2)	-0.2 (± 0.2)		
HDL cholesterol, End of Treatment, n=7, 20	-0.1 (± 0.2)	-0.1 (± 0.2)		
HDL cholesterol, safety follow-up, n=9, 22	-0.1 (± 0.2)	0 (± 0.2)		
LDL cholesterol, Week 4, n=8, 19	0.2 (± 0.3)	0.6 (± 0.5)		
LDL cholesterol, Week 8, n=7, 20	0 (± 0.5)	0.5 (± 0.6)		
LDL cholesterol, Week 12, n=6, 17	-0.1 (± 0.4)	0.6 (± 0.6)		
LDL cholesterol, Week 16, n=5, 16	0 (± 0.5)	0.4 (± 0.5)		
LDL cholesterol, Week 20, n=6, 14	0 (± 0.6)	0.6 (± 0.9)		
LDL cholesterol, End of Treatment, n=7, 20	0 (± 0.4)	0.4 (± 0.6)		
LDL cholesterol, safety follow-up, n=9, 22	0 (± 0.3)	0.3 (± 0.5)		

Notes:

[21] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

[22] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from Baseline in fasted LDL/HDL ratio at Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and at safety follow-up (Week 29)

End point title	Absolute change from Baseline in fasted LDL/HDL ratio at Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and at safety follow-up (Week 29)

End point description:

Change from Baseline is defined as the value at the safety follow up visit minus baseline value.

End point type	Secondary

End point timeframe:

Baseline; Weeks 4, 8, 12, 16, and 20; EOT (Week 24) and safety follow-up (Week 29)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[23]	24[24]		
Units: ratio				
arithmetic mean (standard deviation)				
Baseline, n=7, 22	0 (± 0)	0 (± 0)		
Week 4, n=6, 17	0.3 (± 0.2)	0.7 (± 0.4)		
Week 8, n=6, 18	0.2 (± 0.6)	0.9 (± 0.6)		
Week 12, n=5, 16	0.2 (± 0.4)	0.9 (± 9)		
Week 16, n=5, 15	0.1 (± 0.5)	0.9 (± 0.7)		
Week 20, n=6, 13	0 (± 0.5)	0.7 (± 1.1)		
End of Treatment, n=7, 19	0.1 (± 0.4)	0.5 (± 0.8)		
Safety follow-up, n=7, 20	0.1 (± 0.4)	0.1 (± 0.6)		

Notes:

[23] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

[24] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated shift in the indicated laboratory values from Baseline (BL) to EOT (Week 24)

End point title	Number of participants with the indicated shift in the indicated laboratory values from Baseline (BL) to EOT (Week 24)

End point description:

Laboratory parameters included triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, LDL/HDL ratio, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and amylase and lipase. The central laboratory classified a finding as either abnormal or normal.

End point type	Secondary

End point timeframe:

From Baseline until EOT (Week 24)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[25]	24[26]		
Units: participants				
Triglycerides, BL normal, shift to abnormal	0	2		
Triglycerides, BL abnormal, shift to abnormal	0	0		
Total cholesterol BL normal, shift to abnormal	1	1		
Total cholesterol BL abnormal, shift to abnormal	0	1		
HDL cholesterol BL normal, shift to abnormal	0	1		
HDL cholesterol BL abnormal, shift to abnormal	0	0		
LDL cholesterol BL normal, shift to abnormal	0	0		
LDL cholesterol BL abnormal, shift to abnormal	0	1		
LDL/HDL ratio BL normal, shift to abnormal	0	0		
LDL/HDL ratio BL abnormal, shift to abnormal	0	0		
ALT BL normal, shift to abnormal	0	0		
ALT BL abnormal, shift to abnormal	0	0		
AST BL normal, shift to abnormal	0	0		
AST BL abnormal, shift to abnormal	0	0		
Bilirubin BL normal, shift to abnormal	0	0		
Bilirubin BL abnormal, shift to abnormal	0	0		
Amylase BL normal, shift to abnormal	0	0		
Amylase BL abnormal, shift to abnormal	0	0		
Lipase BL normal, shift to abnormal	0	0		
Lipase BL abnormal, shift to abnormal	0	0		

Notes:

[25] - Safety Population

[26] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Center for Epidemiological Studies Depression Scale (CES-D) scores at Screening; Baseline; Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and safety follow-up (Week 29)

End point title	Summary of Center for Epidemiological Studies Depression Scale (CES-D) scores at Screening; Baseline; Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and safety follow-up (Week 29)

End point description:

The CES-D scale is a short, self-report scale designed to measure depressive symptomatology in the general population. The CES-D consists of 20 questions. Participants were instructed to circle the number for each statement that best described how often they felt or behaved a particular way during the past week. The score was the sum of the weights of the 20 items. Responses range from 0 to 3 for each item (0=rarely or none of the time, 1=some or little of the time, 2=moderately or much of the time, 3=most or almost all the time). The CES-D score ranges from 0 to 60, with higher scores indicating greater depression. Participants with a CES-D score of 20 or higher were re-evaluated within 2 weeks. If a CES-D score of 20 or higher was confirmed on the second occasion, and if the score represents an increase over Baseline of 4 points or more, study treatment was interrupted and the

participants were referred for psychiatric evaluation.

End point type	Secondary

End point timeframe:

Screening; Baseline; Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and safety follow-up (Week 29)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[27]	24[28]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Screening, n=9, 23	7.2 (± 6.6)	5.7 (± 4.7)		
Baseline, n=9, 24	7 (± 5.9)	4.5 (± 5.9)		
Week 4, n=9, 20	5 (± 4.7)	2.9 (± 3.5)		
Week 8, n=7, 20	2.7 (± 2.8)	3.8 (± 6.7)		
Week 12, n=7, 17	4 (± 5.7)	4.2 (± 6.6)		
Week 16, n=6, 16	3.8 (± 4.8)	2.9 (± 5.5)		
Week 20, n=6, 14	4 (± 3.6)	3.6 (± 5.2)		
End of Treatment, n=8, 20	7.4 (± 9)	3 (± 5.4)		
Safety follow up, n=9, 22	4.4 (± 3.9)	4.6 (± 6.7)		

Notes:

[27] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

[28] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from Baseline (BL) in CES-D scores at Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and safety follow-up (Week 29)

End point title	Absolute change from Baseline (BL) in CES-D scores at Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and safety follow-up (Week 29)

End point description:

The CES-D scale is a short, self-report scale designed to measure depressive symptomatology in the general population. The CES-D consists of 20 questions. Participants were instructed to circle the number for each statement that best described how often they felt or behaved a particular way during the past week. The score was the sum of the weights of the 20 items. Responses range from 0 to 3 for each item (0=rarely or none of the time, 1=some or little of the time, 2=moderately or much of the time, 3=most or almost all the time). The CES-D score ranges from 0 to 60, with higher scores indicating greater depression. Participants with a CES-D score of >=20 were re-evaluated within 2 weeks. If a CES-D score of >=20 was confirmed on the second occasion, and if the score represents an increase over BL of 4 points or more, study treatment was interrupted and the participants were referred for psychiatric evaluation. Change from BL is defined as the post-BL value minus the BL value.

End point type	Secondary

End point timeframe:

Baseline; Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and safety follow-up (Week 29)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[29]	24[30]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 4, n=9, 20	-2 (± 2.5)	-0.3 (± 2.4)		
Week 8, n=7, 20	-2.3 (± 2.4)	0.7 (± 7.5)		
Week 12, n=7, 17	-1 (± 2.3)	0.6 (± 5.4)		
Week 16, n=6, 16	-2 (± 2.1)	-0.8 (± 4.7)		
Week 20, n=6, 14	-1.8 (± 3.6)	0.3 (± 4.7)		
End of Treatment, n=8, 20	-0.5 (± 6.6)	-0.6 (± 4.7)		
Safety follow-up, n=9, 22	-2.6 (± 3.9)	0.1 (± 3.4)		

Notes:

[29] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

[30] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Columbia Suicide Severity Rating Scale (CSSRS) scores at Screening; Baseline; Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and safety follow-up (Week 29)

End point title	Summary of Columbia Suicide Severity Rating Scale (CSSRS) scores at Screening; Baseline; Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and safety follow-up (Week 29)

End point description:

The assessment of suicidality was conducted using the CSSRS, a brief questionnaire designed to assess severity and change in suicidality by integrating both behavior and ideation using a semi-structured interview to probe participant responses. The CSSRS was designed to (1) provide definitions of suicidal ideation and behavior and nonsuicidal self-injurious behavior and corresponding probes; (2) quantify the full spectrum of suicidal ideation and suicidal behavior and gauge their severity over specified periods; (3) distinguish suicidal behavior and nonsuicidal self-injurious behavior; and (4) employ a user-friendly format that allows integration of information from multiple sources (e.g., direct participant interview, family and other interviews, and medical records). Participants who scored >3 on the CSSRA were removed from the study and referred for psychiatric evaluation. The CCSRS score ranges from 1 to 5, with a higher score representing increased suicidality.

End point type	Secondary

End point timeframe:

Screening; Baseline; Weeks 4, 8, 12, 16, and 20; EOT (Week 24), and safety follow-up (Week 29)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[31]	24[32]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Screening, n=3, 10	0 (± 0)	0 (± 0)		
Baseline, n=3, 10	0 (± 0)	0 (± 0)		
Week 4, n=3, 09	0 (± 0)	0 (± 0)		
Week 8, n=3, 09	0 (± 0)	0 (± 0)		
Week 12, n=3, 07	0 (± 0)	0 (± 0)		

Week 16, n=2, 07	0 (± 0)	0 (± 0)		
Week 20, n=2, 6	0 (± 0)	0 (± 0)		
End of Treatment, n=2, 7	0 (± 0)	0 (± 0)		
Safety follow up, n=3, 9	0 (± 0)	0 (± 0)		

Notes:

[31] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

[32] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from Baseline in the CSSRS score at Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and safety follow-up (Week 29)

End point title	Absolute change from Baseline in the CSSRS score at Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and safety follow-up (Week 29)

End point description:

The assessment of suicidality was conducted using the CSSRS, a brief questionnaire designed to assess severity and change in suicidality by integrating both behavior and ideation using a semi-structured interview to probe participant responses. The CSSRS was designed to (1) provide definitions of suicidal ideation and behavior and nonsuicidal self-injurious behavior and corresponding probes; (2) quantify the full spectrum of suicidal ideation and suicidal behavior and gauge their severity over specified periods; (3) distinguish suicidal behavior and nonsuicidal self-injurious behavior; and (4) employ a user-friendly format that allows integration of information from multiple sources (e.g., direct participant interview, family and other interviews, and medical records). Participants who scored >3 on the CSSRA were removed from the study and referred for psychiatric evaluation. The CCSRS score ranges from 1 to 5, with a higher score representing increased suicidality.

End point type	Secondary

End point timeframe:

Baseline; Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and safety follow-up (Week 29)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[33]	24[34]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 4, n=3, 9	0 (± 0)	0 (± 0)		
Week 8, n=3, 9	0 (± 0)	0 (± 0)		
Week 12, n=3, 7	0 (± 0)	0 (± 0)		
Week 16, n=2, 7	0 (± 0)	0 (± 0)		
Week 20, n=2, 6	0 (± 0)	0 (± 0)		
End of Treatment, n=2, 7	0 (± 0)	0 (± 0)		
Safety follow-up, n=3, 9	0 (± 0)	0 (± 0)		

Notes:

[33] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

[34] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of systolic blood pressure (SBP) and diastolic blood pressure (DBP) at Screening, Baseline, and EOT (Week 24)

End point title	Summary of systolic blood pressure (SBP) and diastolic blood pressure (DBP) at Screening, Baseline, and EOT (Week 24)

End point description:

SBP and DBP were assessed at Screening, Baseline, and EOT.

End point type	Secondary

End point timeframe:

Screening, Baseline, and EOT (Week 24)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[35]	24[36]		
Units: millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
SBP, Screening, n=9, 23	130.8 (± 13.7)	131.3 (± 16.3)		
SBP, Baseline, n=9, 24	122.8 (± 14)	126.3 (± 16.1)		
SBP, EOT, n=8, 20	122.4 (± 13.7)	128.7 (± 21.4)		
DBP, Screening, n=9, 23	78 (± 10.7)	79.7 (± 9.6)		
DBP, Baseline, n=9, 24	77.4 (± 12.2)	79.1 (± 7.5)		
DBP, EOT, n=8, 20	76 (± 12.2)	75.4 (± 10.5)		

Notes:

[35] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

[36] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of heart rate (HR) at Baseline, Screening, and EOT (Week 24)

End point title	Summary of heart rate (HR) at Baseline, Screening, and EOT (Week 24)

End point description:

HR is defined as the rate at which the heart beats.

End point type	Secondary

End point timeframe:

Screening, Baseline, and EOT (Week 24)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[37]	24[38]		
Units: beats per minute (bpm)				
arithmetic mean (standard deviation)				
Screening, n=9, 23	68.3 (± 6)	74 (± 7.3)		
Baseline, n=9, 24	72.3 (± 6.2)	75.2 (± 8.8)		

EOT, n=8, 20	70.1 (± 6.6)	74.7 (± 7.8)		

Notes:

[37] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

[38] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of body weight at Screening, Baseline ,and EOT (Week 24)

End point title	Summary of body weight at Screening, Baseline ,and EOT (Week 24)

End point description:

Body weight was measured at Screening, Baseline, and EOT.

End point type	Secondary

End point timeframe:

Screening, Baseline, and EOT (Week 24)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[39]	24[40]		
Units: kilograms (kg)				
arithmetic mean (standard deviation)				
Screening, n=9, 24	89.3 (± 15.5)	72.8 (± 12.6)		
Baseline, n=8, 24	89.6 (± 16.6)	72.9 (± 12.9)		
EOT, n=8, 19	88.9 (± 16.5)	73.8 (± 13.4)		

Notes:

[39] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

[40] - Safety Population. Only participants available at the specified time points were analyzed (n=X, X).

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SBP and DBP at EOT (Week 24)

End point title	Change from Baseline in SBP and DBP at EOT (Week 24)

End point description:

Change from Baseline is defined as the value at EOT minus the Baseline value.

End point type	Secondary

End point timeframe:

Baseline and EOT (Week 24)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[41]	20[42]		
Units: mmHg				
arithmetic mean (standard deviation)				
SBP	0.5 (± 12.5)	0.7 (± 19.1)		
DBP	-0.5 (± 9.8)	-4.2 (± 9.8)		

Notes:

[41] - Safety Population. Only those participants available at the specified time points were analyzed.

[42] - Safety Population. Only those participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in heart rate at EOT (Week 24)

End point title	Change from Baseline in heart rate at EOT (Week 24)

End point description:

HR is defined as the rate at which the heart beats. Change from Baseline is defined as the value at EOT minus the Baseline value.

End point type	Secondary

End point timeframe:

Baseline and EOT (Week 24)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[43]	20[44]		
Units: bpm				
arithmetic mean (standard deviation)	-3.1 (± 10.4)	-0.2 (± 10.2)		

Notes:

[43] - Safety Population. Only those participants available at the specified time points were analyzed.

[44] - Safety Population. Only those participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in weight at EOT (Week 24)

End point title	Change from Baseline in weight at EOT (Week 24)

End point description:

Change from Bseline is defined as the value at EOT minus the value at Baseline.

End point type	Secondary

End point timeframe:

Baseline and EOT (Week 24)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[45]	19[46]		
Units: kg				
arithmetic mean (standard deviation)	-0.8 (± 3.2)	-0.5 (± 1.4)		

Notes:

[45] - Safety Population. Only those participants available at the specified time points were analyzed.

[46] - Safety Population. Only those participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with normal/abnormal physical status at Baseline with a worst post-Baseline finding of normal/abnormal

End point title	Number of participants with normal/abnormal physical status at Baseline with a worst post-Baseline finding of normal/abnormal

End point description:

A physical examination for each participant was performed at Baseline and at EOT (Week 24). The primary investigator classified physical status as either normal or abnormal.

End point type	Secondary

End point timeframe:

Baseline and EOT (Week 24)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[47]	24[48]		
Units: participants				
Baseline normal, worst post-Baseline normal	6	18		
Baseline normal, worst post-Baseline abnormal	1	0		
Baseline abnormal, worst post-Baseline normal	1	1		
Baseline abnormal, worst post-Baseline abnormal	0	0		

Notes:

[47] - Safety Population

[48] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with a negative serum pregnancy test at Screening; Baseline; Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and safety follow-up (Week 29)

End point title	Number of participants with a negative serum pregnancy test at Screening; Baseline; Weeks 4, 8, 12, 16, and 20; EOT (Week 24); and safety follow-up (Week 29)

End point description:

Serum pregnancy tests were performed at each visit for females of childbearing potential.

End point type	Secondary

End point timeframe:

Screening; Baseline; Weeks 4, 8, 12, 16, and 20; EOT (Week 24); safety follow-up (Week 29)

End point values	Matching placebo	Alitretinoin 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[49]	24[50]		
Units: participants				
Screening	4	7		
Baseline	4	7		
Week 4	4	4		
Week 8	3	4		
Week 12	3	3		
Week 16	3	2		
Week 20	2	2		
EOT	4	4		
Safety follow-up	4	5		

Notes:

[49] - Safety Population

[50] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

A treatment-emergent adverse event (AE) is defined as any adverse change that occured after treatment commenced and up to 7 days post-treatment.

Adverse event reporting additional description:

Serious adverse events (SAEs) and non-serious AEs were reported for members of the Safety Population, comprised of all randomized participants who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Matching placebo

Reporting group description:

Participants received matching placebo orally QD for up to 24 weeks.

Reporting group title	Alitretinoin 30 mg

Reporting group description:

Participants received an alitretinoin 30 mg capsule orally QD for up to 24 weeks.

Serious adverse events	Matching placebo	Alitretinoin 30 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Matching placebo	Alitretinoin 30 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 9 (88.89%)	16 / 24 (66.67%)	
Vascular disorders			
Haematoma			

subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Discomfort			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Suicidal ideation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood triglycerides increased			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Low-density lipoprotein/high-density lipoprotein ratio increased			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Low-density lipoprotein increased			

subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Blood potassium increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 9 (22.22%)	8 / 24 (33.33%)	
occurrences (all)	3	11	
Gastrointestinal disorders			
Cheilitis			
subjects affected / exposed	1 / 9 (11.11%)	3 / 24 (12.50%)	
occurrences (all)	1	3	
Nausea			
subjects affected / exposed	1 / 9 (11.11%)	2 / 24 (8.33%)	
occurrences (all)	1	4	
Diarrhoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatic fibrosis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Granuloma annulare			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Pigmentation disorder			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

Pruritus			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 9 (22.22%)	1 / 24 (4.17%)	
occurrences (all)	3	2	
Pain in extremity			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Joint swelling			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 9 (11.11%)	7 / 24 (29.17%)	
occurrences (all)	1	10	
Bronchitis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 9 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	4	
Gout			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 January 2011	Change in exclusion criteria: patient safety, clarity Study assessment: Revision laboratory safety test
20 November 2011	CES-D Questionnaire: To provide more specific guidance on psychiatric referral Change in exclusion criteria: To remove ambiguity and improve clarity and uniform understanding across study centers
06 February 2013	Change of sponsor, change in inclusion/exclusion criteria: scientific evidence, patient safety

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported