Clinical trial results:
A Phase IIa, Open-Label, Multiple Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Exploratory Efficacy of Vamorolone in Boys with Duchenne Muscular Dystrophy (DMD)

Summary

EudraCT number	2016-004262-26
Trial protocol	SE GB
Global end of trial date	01 May 2018

Results information

Result version number	v1 (current)
This version publication date	19 October 2018
First version publication date	19 October 2018

Trial information

Trial identification

Sponsor protocol code	VBP15-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02760264
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ReveraGen BioPharma Inc.
Sponsor organisation address	155 Gibbs Street Suite 433, Rockville, United States, 20850
Public contact	Vice President, Operations, ReveraGen BioPharma Inc., +1 215 680 8286, jesse.damsker@reveragen.com
Scientific contact	Vice President, Operations, ReveraGen BioPharma Inc., +1 215 680 8286, jesse.damsker@reveragen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001794-PIP02-16
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	01 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 May 2018
Global end of trial reached?	Yes
Global end of trial date	01 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of multiple ascending oral doses of vamorolone in ambulant boys ages 4-< 7 years with DMD.

Protection of trial subjects:

This study was conducted in accordance with the principles of the 18th World Medical Assembly (Helsinki, June 1964), and amendments of the 29th (Tokyo, 1975), 35th (Venice, 1983), 41st (Hong Kong, 1989), 48th (Somerset West, 1996), 52nd (Edinburgh, 2000), 53rd (Washington, 2002), 55th (Tokyo, 2004), 59th (Seoul, 2008), and 64th (Fortaleza, 2013) World Medical Assemblies.

Further, the trial was conducted in accordance with:

-International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP)

-The United States (US) Food and Drug Administration (FDA) Code of Federal Regulations, Title 21 CFR Part 312 - IND Application, Part 50 - Protection of Human Patients with particular focus in SubPart D, and/or Part 56 - Institutional Review Boards

-US Health Insurance Portability and Accountability Act of 1996 (HIPAA)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 20
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Israel: 5
Worldwide total number of subjects	48
EEA total number of subjects	10

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)	48
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were screened based on inclusion and exclusion criteria specified in the VBP15-002 protocol

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dose level group 1

Arm description:

0.25 mg/kg/day for 14 days

Arm type	Experimental
Investigational medicinal product name	Vamorolone 4% oral suspension
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Study drug was administered by mouth using a volumetric syringe. Following administration of the dose of study drug, the syringe was filled once with water and the water was administered by mouth using the volumetric syringe. The subject then drank approximately 50 mL (approximately 2 ounces) of water to ensure the full dose had been ingested.

Arm title	Dose level group 2

Arm description:

0.75 mg/kg/day for 14 days

Arm type	Experimental
Investigational medicinal product name	Vamorolone 4% oral suspension
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Study drug was administered by mouth using a volumetric syringe. Following administration of the dose of study drug, the syringe was filled once with water and the water was administered by mouth using the volumetric syringe. The subject then drank approximately 50 mL (approximately 2 ounces) of water to ensure the full dose had been ingested.

Arm title	Dose level group 3

Arm description:

2.0 mg/kg/day for 14 days

Arm type	Experimental

Investigational medicinal product name	Vamorolone 4% oral suspension
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Study drug was administered by mouth using a volumetric syringe. Following administration of the dose of study drug, the syringe was filled once with water and the water was administered by mouth using the volumetric syringe. The subject then drank approximately 50 mL (approximately 2 ounces) of water to ensure the full dose had been ingested.

Arm title	Dose level group 4

Arm description:

6.0 mg/kg/day for 14 days

Arm type	Experimental
Investigational medicinal product name	Vamorolone 4% oral suspension
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Study drug was administered by mouth using a volumetric syringe. Following administration of the dose of study drug, the syringe was filled once with water and the water was administered by mouth using the volumetric syringe. The subject then drank approximately 50 mL (approximately 2 ounces) of water to ensure the full dose had been ingested.

Number of subjects in period 1	Dose level group 1	Dose level group 2	Dose level group 3
Started	12	12	12
Completed	12	12	12

Number of subjects in period 1	Dose level group 4
Started	12
Completed	12

Baseline characteristics

Reporting groups	
Reporting group title	Dose level group 1
Reporting group description: 0.25 mg/kg/day for 14 days	
Reporting group title	Dose level group 2
Reporting group description: 0.75 mg/kg/day for 14 days	
Reporting group title	Dose level group 3
Reporting group description: 2.0 mg/kg/day for 14 days	
Reporting group title	Dose level group 4
Reporting group description: 6.0 mg/kg/day for 14 days	

Reporting group values	Dose level group 1	Dose level group 2	Dose level group 3
Number of subjects	12	12	12
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)	12	12	12
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	0	0	0
Male	12	12	12

Reporting group values	Dose level group 4	Total	
Number of subjects	12	48	
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)	12	48	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	

85 years and over	0	0	

Gender categorical Units: Subjects			
Female	0	0	
Male	12	48	

End points

End points reporting groups

Reporting group title	Dose level group 1
Reporting group description: 0.25 mg/kg/day for 14 days	
Reporting group title	Dose level group 2
Reporting group description: 0.75 mg/kg/day for 14 days	
Reporting group title	Dose level group 3
Reporting group description: 2.0 mg/kg/day for 14 days	
Reporting group title	Dose level group 4
Reporting group description: 6.0 mg/kg/day for 14 days	

Primary: Overall Summary of Adverse Events as Assessed by CTCAE Version 4.03

End point title	Overall Summary of Adverse Events as Assessed by CTCAE Version 4.03[1]

End point description:

Treatment-emergent adverse events (TEAEs) are defined as any adverse event or worsening of an existing conditions after initiation of the investigational product and through the subject's last study visit (study completion or early termination). Serious adverse events were recorded for up to 30 days after the final administration of study drug. Related TEAEs include those considered possibly, probably, and definitely related.

End point type	Primary

End point timeframe:

Adverse events will be recorded from the date of informed consent and through the time of the subject’s last study visit. Serious adverse events will be recorded from the date of informed consent and for up to 30 days after final drug administration.

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: Safety analyses will be performed using the Safety Population and were completed using the actual treatment a subject received and will address the primary objective of the study.

Treatment levels were not compared.

End point values	Dose level group 1	Dose level group 2	Dose level group 3	Dose level group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	12	12
Units: Number of Participants				
Total Number of Adverse Events	16	18	13	11
Total Number of Treatment Emergent Adverse Events	13	13	11	9
Any TEAE	7	6	8	7
Any Drug Related TEAE	1	2	2	3
Any CTCAE Grade 3 or higher	0	0	0	0
Discontinuation of Study Drug due to a TEAE	0	0	0	0
Any Serious TEAE	0	0	0	0

Death	0	0	0	0

Attachments (see zip file)	Summary of Adverse Events Overall.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Pharmacodynamic Biomarkers (Bone Turnover) Osteocalcin

End point title	Serum Pharmacodynamic Biomarkers (Bone Turnover) Osteocalcin

End point description:

Pharmacodynamic biomarkers were measured to investigate the effects of single and multiple oral doses of vamorolone on serum PD biomarkers in ambulant boys ages 4-< 7 years with DMD.

End point type	Secondary

End point timeframe:

Baseline
Day 1
Week 2
Week 4

End point values	Dose level group 1	Dose level group 2	Dose level group 3	Dose level group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	12	12
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline	37.94 (± 11.622)	35.66 (± 6.800)	41.17 (± 5.617)	44.36 (± 5.979)
Day 1	39.37 (± 14.189)	35.89 (± 7.526)	34.93 (± 6.881)	33.52 (± 9.135)
Day 1 Change from Baseline	1.43 (± 8.197)	0.23 (± 5.304)	-6.23 (± 10.930)	-11.37 (± 9.137)
Day 1 Percent Change from Baseline	3.95 (± 22.015)	1.41 (± 15.449)	-12.63 (± 25.020)	-25.05 (± 20.228)
Week 2	38.53 (± 12.025)	35.10 (± 8.238)	37.51 (± 8.624)	29.04 (± 4.853)
Week 2 Change from Baseline	0.58 (± 5.986)	-0.56 (± 7.934)	-3.66 (± 9.818)	-15.32 (± 6.450)
Week 2 Percent change from Baseline	2.48 (± 16.756)	-0.07 (± 22.408)	-7.81 (± 23.644)	-33.87 (± 12.548)
Week 4	39.20 (± 14.136)	42.24 (± 8.426)	47.91 (± 6.648)	42.81 (± 10.851)
Week 4 Change from Baseline	1.26 (± 5.650)	6.58 (± 9.341)	6.74 (± 9.747)	-1.55 (± 11.176)
Week 4 Percent Change from Baseline	2.72 (± 14.063)	20.91 (± 28.644)	18.74 (± 25.095)	-2.43 (± 25.932)

Attachments (see zip file)	Osteocalcin.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Pharmacodynamic Biomarkers (Bone Turnover) Procollagen 1 N-Terminal Propeptide

End point title	Serum Pharmacodynamic Biomarkers (Bone Turnover) Procollagen 1 N-Terminal Propeptide

End point description:

Pharmacodynamic biomarkers were measured to investigate the effects of single and multiple oral doses of vamorolone on serum PD biomarkers in ambulant boys ages 4-< 7 years with DMD.

End point type	Secondary

End point timeframe:

Baseline
Day 1
Week 2
Week 4

End point values	Dose level group 1	Dose level group 2	Dose level group 3	Dose level group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	12	12
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline	555.8 (± 184.72)	480.7 (± 118.20)	508.2 (± 94.36)	511.5 (± 106.50)
Day 1	474.0 (± 116.45)	443.7 (± 112.38)	417.1 (± 87.35)	475.2 (± 147.10)
Day 1 Change from Baseline	-81.8 (± 124.24)	-34.5 (± 101.97)	-91.1 (± 64.64)	-36.5 (± 144.04)
Day 1 Percent Change from Baseline	-12.2 (± 17.07)	-5.4 (± 24.58)	-17.4 (± 12.59)	-5.7 (± 30.76)
Week 2	443.8 (± 93.86)	407.8 (± 96.54)	346.6 (± 68.59)	303.7 (± 56.38)
Week 2 Change from Baseline	-112.0 (± 125.08)	-70.6 (± 123.69)	-161.6 (± 73.52)	-207.8 (± 78.16)
Week 2 Percent Change from Baseline	-17.5 (± 14.65)	-11.2 (± 29.19)	-30.9 (± 11.80)	-39.9 (± 9.22)
Week 4	573.8 (± 251.02)	496.7 (± 117.57)	492.0 (± 81.92)	566.3 (± 149.32)
Week 4 Change from Baseline	18.1 (± 153.10)	21.3 (± 122.87)	-16.2 (± 79.64)	54.8 (± 118.09)
Week 4 Percent Change from Baseline	2.8 (± 25.57)	7.8 (± 30.86)	-1.4 (± 17.47)	11.8 (± 28.24)

Attachments (see zip file)	Procollagen 1 N-Terminal Propeptide.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Pharmacodynamic Biomarkers (Bone Turnover) Type I Collagen C-Telopeptides

End point title	Serum Pharmacodynamic Biomarkers (Bone Turnover) Type I Collagen C-Telopeptides

End point description:

Pharmacodynamic biomarkers were measured to investigate the effects of single and multiple oral doses of vamorolone on serum PD biomarkers in ambulant boys ages 4-< 7 years with DMD.

End point type	Secondary

End point timeframe:

Baseline, Day 1, Week 4

End point values	Dose level group 1	Dose level group 2	Dose level group 3	Dose level group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	12	12
Units: pg/mL				
arithmetic mean (standard deviation)				
Baseline	871.0 (± 160.85)	935.8 (± 286.50)	936.8 (± 256.25)	889.3 (± 186.68)
Day 1	974.8 (± 252.77)	940.8 (± 227.60)	838.3 (± 233.30)	786.8 (± 331.68)
Day 1 Change from Baseline	72.4 (± 241.87)	-12.9 (± 233.44)	-98.5 (± 237.69)	-115.7 (± 421.04)
Day 1 Percent change from Baseline	9.9 (± 25.38)	2.7 (± 23.76)	-8.0 (± 23.93)	-6.7 (± 53.72)
Week 2	963.7 (± 157.68)	903.3 (± 251.01)	710.4 (± 180.03)	625.7 (± 203.19)
Week 2 Change from Baseline	85.0 (± 185.90)	-19.9 (± 266.99)	-226.4 (± 185.99)	-263.7 (± 229.69)
Week 2 Percent Change from Baseline	11.9 (± 20.52)	2.2 (± 26.44)	-22.5 (± 15.27)	-27.7 (± 26.50)
Week 4	915.9 (± 263.13)	983.5 (± 298.47)	949.8 (± 303.76)	989.2 (± 216.29)
Week 4 Change from Baseline	17.4 (± 267.45)	34.8 (± 271.50)	12.9 (± 181.45)	99.8 (± 211.90)
Week 4 Percent Change from Baseline	3.6 (± 28.96)	6.8 (± 34.06)	2.7 (± 19.03)	14.5 (± 32.98)

Attachments (see zip file)	Type I Collagen C-Telopeptides.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Pharmacodynamic Biomarkers (Insulin Resistance) Fasting Glucose

End point title	Serum Pharmacodynamic Biomarkers (Insulin Resistance) Fasting Glucose

End point description:

Pharmacodynamic biomarkers were measured to investigate the effects of single and multiple oral doses of vamorolone on serum PD biomarkers in ambulant boys ages 4-< 7 years with DMD.

End point type	Secondary

End point timeframe:

Baseline, Week 2

End point values	Dose level group 1	Dose level group 2	Dose level group 3	Dose level group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	12	12
Units: mg/ dL				
arithmetic mean (standard deviation)				
Baseline	87.5 (± 9.44)	88.9 (± 18.71)	89.3 (± 7.91)	92.3 (± 8.19)
Week 2	85.3 (± 9.29)	83.1 (± 6.69)	89.5 (± 5.20)	89.2 (± 11.12)
Week 2 Change from Baseline	-2.2 (± 10.46)	-5.8 (± 18.92)	0.2 (± 8.79)	-1.3 (± 9.41)
Week 2 Percent Change from Baseline	-1.8 (± 13.07)	-4.2 (± 13.98)	0.8 (± 9.76)	-1.2 (± 9.80)

Attachments (see zip file)	Fasting Glucose.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Pharmacodynamic Biomarkers (Insulin Resistance) Insulin

End point title	Serum Pharmacodynamic Biomarkers (Insulin Resistance) Insulin

End point description:

End point type	Secondary

End point timeframe:

Baseline , Week 2

End point values	Dose level group 1	Dose level group 2	Dose level group 3	Dose level group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	12	12
Units: µIU/mL				
arithmetic mean (standard deviation)				
Baseline	5.54 (± 3.651)	3.09 (± 2.033)	3.40 (± 1.548)	3.96 (± 2.027)
Week 2	5.29 (± 2.671)	3.22 (± 1.924)	3.87 (± 2.118)	6.73 (± 4.599)
Week 2 Change from Baseline	-0.65 (± 2.913)	0.34 (± 1.289)	0.47 (± 2.777)	2.78 (± 4.651)
Week 2 Percent Change from Baseline	-5.54 (± 32.622)	26.07 (± 76.483)	42.85 (± 107.337)	83.55 (± 117.064)

Attachments (see zip file)	Insulin.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Pharmacodynamic Biomarkers (Adrenal Axis Suppression) First in Morning Cortisol

End point title	Serum Pharmacodynamic Biomarkers (Adrenal Axis Suppression) First in Morning Cortisol

End point description:

Pharmacodynamic biomarkers were measured to investigate the effects of single and multiple oral doses of vamorolone on serum PD biomarkers in ambulant boys ages 4-< 7 years with DMD.

End point type	Secondary

End point timeframe:

Week 2 (pre-dose)

End point values	Dose level group 1	Dose level group 2	Dose level group 3	Dose level group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	11	11	10
Units: mcg/dL				
arithmetic mean (standard deviation)				
Week 2 (pre-dose)	10.425 (± 1.7358)	9.755 (± 2.7614)	7.321 (± 3.0322)	3.010 (± 1.0141)

Attachments (see zip file)	First in Morning Cortisol.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Metabolites in Safety Testing (MIST)

End point title	Metabolites in Safety Testing (MIST)[2]

End point description:

A portion of each blood sample collected for PK testing at each of the Week 2 (Day 14) assessment time points will be used for analysis of vamorolone metabolites. The relative exposures of the metabolites observed in human plasma were obtained to determine if any metabolite exceeded the 10% total drug related exposure (TDRE) threshold specified by the FDA and ICH guidance documents.

End point type	Secondary

End point timeframe:

Week 2 (Day 14)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Percent total drug related exposures for each metabolite in each sample were calculated by dividing the average area ratio for each metabolite by the sum of the average area ratios for all metabolites and Vamorolone in that sample.

Treatment levels were not compared.

End point values	Dose level group 3			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Average % of total drug related exposure				
arithmetic mean (standard deviation)				
M1	34.42 (± 2.79)			
M2	1.16 (± 0.06)			
M3	1.21 (± 0.07)			
M4	37.84 (± 3.78)			
M5	2.73 (± 0.17)			
Vamorolone	22.64 (± 0.69)			

Attachments (see zip file)	MIST Average % of total drug related exposure.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Assessments (Cmax)

End point title	Pharmacokinetic (PK) Assessments (Cmax)

End point description:

Plasma concentrations of vamorolone were measured using a specific and validated liquid chromatography tandem mass spectrometry (LC-MS) assay. Cmax= maximum concentration.

End point type	Secondary

End point timeframe:

Day 1, Week 2

End point values	Dose level group 1	Dose level group 2	Dose level group 3	Dose level group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	12	12	12
Units: Cmax (ng/mL)				
arithmetic mean (standard deviation)				
Day 1	22.9 (± 13.4)	75.9 (± 25.9)	199 (± 111)	855.6 (± 471)
Week 2	32.2 (± 15.2)	124.7 (± 42.5)	252.5 (± 96)	970 (± 270)

Attachments (see zip file)	PK Vamorolone.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Assessments (tmax)

End point title	Pharmacokinetic (PK) Assessments (tmax)

End point description:

Plasma concentrations of vamorolone were measured using a specifc and validated liquid chromatography tandem mass spectrometry (LC-MS) assay. tmax= time when plasma concentration is at maximum.

End point type	Secondary

End point timeframe:

Day 1,
Week 2

End point values	Dose level group 1	Dose level group 2	Dose level group 3	Dose level group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	12	12	12
Units: hour				
arithmetic mean (standard deviation)				
Day 1	3.6 (± 1.2)	4.6 (± 2.1)	2.5 (± 1.3)	2.7 (± 1.3)
Week 2	3.8 (± 1.80)	3.8 (± 2.2)	2.8 (± 1)	2.3 (± 0.86)

Attachments (see zip file)	PK Vamorolone.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Assessments (AUC inf)

End point title	Pharmacokinetic (PK) Assessments (AUC inf)

End point description:

Plasma concentrations of vamorolone were measured using a specific and validated liquid chromatography tandem mass spectrometry (LC-MS) assay. AUC inf= Area under the concentration vs. time curve to time infinity.

End point type	Secondary

End point timeframe:

Day 1,
Week 2

End point values	Dose level group 1	Dose level group 2	Dose level group 3	Dose level group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	12	12	12
Units: [(hr)(ng)/mL]				
arithmetic mean (standard deviation)				
Day 1	118 (± 48)	379 (± 117)	761 (± 352)	3279 (± 1693)
Week 2	164 (± 61)	544 (± 155)	1138 (± 467)	3606 (± 897)

Attachments (see zip file)	PK Vamorolone.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Assessments t(1/2)

End point title	Pharmacokinetic (PK) Assessments t(1/2)

End point description:

Plasma concentrations of vamorolone were measured using a specific and validated liquid chromatography tandem mass spectrometry (LC-MS) assay. t1/2= elimination half life

End point type	Secondary

End point timeframe:

Day 1,
Week 2

End point values	Dose level group 1	Dose level group 2	Dose level group 3	Dose level group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	12	12	12
Units: hour				
arithmetic mean (standard deviation)				
Day 1	2.1 (± 0.85)	1.8 (± 0.43)	1.9 (± 0.79)	1.9 (± 0.95)
Week 2	1.9 (± 0.96)	2.1 (± 0.8)	1.9 (± 1.02)	1.4 (± 0.35)

Attachments (see zip file)	PK Vamorolone.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Assessments CL (ml/hr/kg)

End point title	Pharmacokinetic (PK) Assessments CL (ml/hr/kg)

End point description:

Plasma concentrations of vamorolone were measured using a specific and validated liquid chromatography tandem mass spectrometry (LC-MS) assay. CL= clearance

End point type	Secondary

End point timeframe:

Day 1,
Week 2

End point values	Dose level group 1	Dose level group 2	Dose level group 3	Dose level group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	12	12	12
Units: ml/hr/kg				
arithmetic mean (standard deviation)				
Day 1	2459 (± 897)	2285 (± 1103)	2697 (± 1285)	2320 (± 1375)
Week 2	1828 (± 919)	1509 (± 482)	2047 (± 771)	1777 (± 476)

Attachments (see zip file)	PK Vamorolone.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events will be recorded from the date of informed consent and through the time of the subject's last study visit. Serious adverse events will be recorded from the date of informed consent and for up to 30 days after final drug administration.

Adverse event reporting additional description:

The incidence of TEAEs will be summarized by dose level, SOC and preferred term; dose level, SOC, and intensity (CTCAE grade; CTCAE version 4.03); dose level, SOC, and outcome; and dose level, SOC and relationship to study drug.

No serious treatment emergent adverse events
No subjects with all-cause mortality.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Dose level group 1
Reporting group description: -	
Reporting group title	Dose level group 2
Reporting group description: -	
Reporting group title	Dose level group 3
Reporting group description: -	
Reporting group title	Dose level group 4

Reporting group description: -

Serious adverse events	Dose level group 1	Dose level group 2	Dose level group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events		0	0

Serious adverse events	Dose level group 4		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Dose level group 1	Dose level group 2	Dose level group 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)	6 / 12 (50.00%)	8 / 12 (66.67%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Faeces discoloured			

subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Lip swelling			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	2 / 12 (16.67%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 12 (0.00%)	2 / 12 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Rash macular			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Emotional Disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Irritability			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Restlessness			

subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 12 (0.00%)	3 / 12 (25.00%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Enterobiasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Lice infestation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 12 (25.00%)	2 / 12 (16.67%)	1 / 12 (8.33%)
occurrences (all)	3	2	1

Non-serious adverse events	Dose level group 4		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)		
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Lethargy			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Faeces discoloured			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Lip swelling			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		

Vomiting			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Upper-airway cough syndrome			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Rash macular			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Emotional Disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Irritability			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Restlessness			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Chromaturia			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Enterobiasis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gastroenteritis viral			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Lice infestation			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30219580