Clinical trial results:
Randomized, controlled, double-blind, multi-center trial to evaluate the efficacy and safety of an Etofenamate 5% cutaneous patch vs. Placebo in the treatment of acute uncomplicated unilateral ankle sprain

Summary

EudraCT number	2016-000252-99
Trial protocol	DE
Global end of trial date	27 April 2017

Results information

Result version number	v1 (current)
This version publication date	13 May 2018
First version publication date	13 May 2018

Trial information

Trial identification

Sponsor protocol code	DRO-200/III/15/1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Drossapharm AG
Sponsor organisation address	Birsweg 1, Arlesheim, Switzerland, 4144
Public contact	Dr. Roger Imboden, Drossapharm AG, 0041 617051000, roger.imboden@drossapharm.ch
Scientific contact	Dr. Roger Imboden, Drossapharm AG, 0041 617051000, roger.imboden@drossapharm.ch

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	09 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 April 2017
Global end of trial reached?	Yes
Global end of trial date	27 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of an Etofenamate 5% cutaneous patch applied two times a day compared with a placebo patch in patients with acute ankle sprains, in particular with regard to pain relief.

Protection of trial subjects:

Patients were monitored throughout participation in the study for adverse events.

Background therapy:

As necessary: Use of a crutch, exercise(Achilles' tendon stretching), muscle strengthening exercises only after range of motion has been regained. Standard care by rest, ice, compression (non-occlusive bandage), or elevation (RICE) at the discretion of the Investigator. Rescue medication (paracetamol) except for the 6 hours prior to Visit 4 (48 h), Visit 5 (72 h) and Visit 6 (96 h).

Evidence for comparator:

Placebo patch was indistinguishable from the investigational drug etofenamate 5% cutaneous patch.

Actual start date of recruitment	03 September 2016
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: 156
Worldwide total number of subjects	156
EEA total number of subjects	156

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)	156
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled in the clinical trial by five investigators in Germany. To qualify for participation, patients had to experience an acute Grade I or II sprain of the ankle within the previous 12 hours. Patients were to be randomized as soon as possible after the injury.

Pre-assignment

Screening details:

To minimize unnecessary risks to patients they were to be screened at baseline to ensure absence of the various clinical disorders described in the exclusion criteria. This process included a baseline physical examination, vital signs, medical and drug history.

Period 1

Period 1 title	Overall trial (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

Blinding implementation details:

Patients were treated with etofenamate 5% cutaneous patch or with a matching placebo patch.

Arms

Are arms mutually exclusive?	Yes
Arm title	Etofenamate 5% cutaneous patch

Arm description:

Patients were treated with a cutaneous patch containing 5% etofenamate.

Arm type	Experimental
Investigational medicinal product name	Etofenamate 5% cutaneous patch
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

The patch was applied twice daily for 7 days.

Arm title	Placebo

Arm description:

Patients were treated with a matching placebo patch.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Cutaneous use

Dosage and administration details:

The patch was applied twice daily for 7 days.

Number of subjects in period 1	Etofenamate 5% cutaneous patch	Placebo
Started	78	78
Completed	78	78

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	156	156	
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)	156	156	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
According to the study protocol patients ages 18-60 years could be enrolled.			
Units: years			
arithmetic mean	35.3		
standard deviation	± 11.8	-	
Gender categorical Units: Subjects			
Female	64	64	
Male	92	92	

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS) etofenamate 5% cutaneous patch
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS includes all randomized patients who received at least one dose of IMP. The FAS population is the primary population for the analysis of efficacy. The intention-to-treat (ITT) population is identical to the full analysis set (FAS).

Subject analysis set title	Full Analysis Set (FAS) placebo patch
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS includes all randomized patients who received at least one dose of study treatment. The FAS population is the primary population for the analysis of efficacy. The intention-to-treat (ITT) population is identical to the full analysis set (FAS).

Reporting group values	Full Analysis Set (FAS) etofenamate 5% cutaneous patch	Full Analysis Set (FAS) placebo patch	
Number of subjects	78	78	

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)	78	78	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
According to the study protocol patients ages 18-60 years could be enrolled.			
Units: years			
arithmetic mean	33.8	36.9	
standard deviation	± 11.6	± 11.9	
Gender categorical Units: Subjects			
Female	28	36	
Male	50	42	

End points

End points reporting groups

Reporting group title	Etofenamate 5% cutaneous patch
Reporting group description:	
Patients were treated with a cutaneous patch containing 5% etofenamate.	
Reporting group title	Placebo
Reporting group description:	
Patients were treated with a matching placebo patch.	
Subject analysis set title	Full Analysis Set (FAS) etofenamate 5% cutaneous patch
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS includes all randomized patients who received at least one dose of IMP. The FAS population is the primary population for the analysis of efficacy. The intention-to-treat (ITT) population is identical to the full analysis set (FAS).	
Subject analysis set title	Full Analysis Set (FAS) placebo patch
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS includes all randomized patients who received at least one dose of study treatment. The FAS population is the primary population for the analysis of efficacy. The intention-to-treat (ITT) population is identical to the full analysis set (FAS).	

Primary: Ankle pain-on-movement (POM)

End point title	Ankle pain-on-movement (POM)
End point description:	
Ankle-pain on movement was assessed in mm using a 100 mm Visual Analogue Scale (VAS) (0 mm = ‘no pain’, and 100 mm = ‘extreme pain’).	
End point type	Primary
End point timeframe:	
Assessed at Visit 5 (72 hours after initiation of treatment).	

End point values	Etofenamate 5% cutaneous patch	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	78		
Units: mm				
arithmetic mean (standard deviation)	36.3 (± 21.8)	57.4 (± 16.1)		

Statistical analyses

Statistical analysis title	ANCOVA
Statistical analysis description:	
For quantitative efficacy outcomes assessed at the clinical trial sites (pain-on-movement, pain-at rest, ankle swelling) and derived outcomes (area-under-the-curve) null hypotheses were tested with an analysis of covariance (ANCOVA) model. For comparisons using the specified ANCOVA models above, the least square mean for each treatment and the corresponding difference between least square means (EFM 5% patch - Placebo) with the p-value and 95% confidence interval were presented from the model.	

Comparison groups	Etofenamate 5% cutaneous patch v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least square mean
Point estimate	22.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.2
upper limit	26
Variability estimate	Standard deviation

Secondary: Ankle-pain on movement at visit 4

End point title	Ankle-pain on movement at visit 4

End point description:

Ankle-pain on movement was assessed in mm using a 100 mm Visual Analogue Scale (VAS) (0 mm = 'no pain', and 100 mm = 'extreme pain').

End point type	Secondary

End point timeframe:

Assessed at Visit 4 (48 hours after initiation of treatment).

End point values	Etofenamate 5% cutaneous patch	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	78		
Units: mm				
arithmetic mean (standard deviation)	46.5 (± 22.3)	62.8 (± 14.8)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

For quantitative efficacy outcomes assessed at the clinical trial sites (pain-on-movement, pain-at rest, ankle swelling) and derived outcomes (area-under-the-curve) null hypotheses were tested with an analysis of covariance (ANCOVA) model. For comparisons using the specified ANCOVA models above, the least square mean for each treatment and the corresponding difference between least square means (EFM 5% patch - Placebo) with the p-value and 95% confidence interval were presented from the model.

Comparison groups	Etofenamate 5% cutaneous patch v Placebo

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least square mean
Point estimate	17.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.5
upper limit	21.3
Variability estimate	Standard deviation

Secondary: Ankle-pain on movement at Visit 6

End point title	Ankle-pain on movement at Visit 6

End point description:

Ankle-pain on movement was assessed in mm using a 100 mm Visual Analogue Scale (VAS) (0 mm = 'no pain', and 100 mm = 'extreme pain').

End point type	Secondary

End point timeframe:

Assessed at Visit 6 (96 hours after initiation treatment).

End point values	Etofenamate 5% cutaneous patch	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	78		
Units: mm				
arithmetic mean (standard deviation)	27.9 (± 21.6)	50.1 (± 17.4)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

For quantitative efficacy outcomes assessed at the clinical trial sites (pain-on-movement, pain-at rest, ankle swelling) and derived outcomes (area-under-the-curve) null hypotheses were tested with an analysis of covariance (ANCOVA) model. For comparisons using the specified ANCOVA models above, the least square mean for each treatment and the corresponding difference between least square means (EFM 5% patch - Placebo) with the p-value and 95% confidence interval were presented from the model.

Comparison groups	Etofenamate 5% cutaneous patch v Placebo

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least square mean
Point estimate	23
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.9
upper limit	27.1
Variability estimate	Standard deviation

Secondary: Ankle-pain on movemement at Visit 7

End point title	Ankle-pain on movemement at Visit 7

End point description:

Ankle-pain on movement was assessed in mm using a 100 mm Visual Analogue Scale (VAS) (0 mm = 'no pain', and 100 mm = 'extreme pain').

End point type	Secondary

End point timeframe:

Assessed at Visit 7 (Day 8 (±1) after initiation of treatment.

End point values	Etofenamate 5% cutaneous patch	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	78		
Units: mm				
arithmetic mean (standard deviation)	12.8 (± 13.5)	31.2 (± 17.9)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

For quantitative efficacy outcomes assessed at the clinical trial sites (pain-on-movement, pain-at rest, ankle swelling) and derived outcomes (area-under-the-curve) null hypotheses were tested with an analysis of covariance (ANCOVA) model. For comparisons using the specified ANCOVA models above, the least square mean for each treatment and the corresponding difference between least square means (EFM 5% patch - Placebo) with the p-value and 95% confidence interval were presented from the model.

Comparison groups	Etofenamate 5% cutaneous patch v Placebo

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least square mean
Point estimate	19.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.8
upper limit	23.4
Variability estimate	Standard deviation

Secondary: Ankle-pain at rest at Visit 5

End point title	Ankle-pain at rest at Visit 5

End point description:

Ankle-pain at rest was assessed in mm using a 100 mm Visual Analogue Scale (VAS) (0 mm = 'no pain', and 100 mm = 'extreme pain').

End point type	Secondary

End point timeframe:

Assessed at Visit 5 (72 h after initiation of treatment)

End point values	Etofenamate 5% cutaneous patch	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	78		
Units: mm				
arithmetic mean (standard deviation)	12.5 (± 12.6)	17.9 (± 15.0)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

For quantitative efficacy outcomes assessed at the clinical trial sites (pain-on-movement, pain-at rest, ankle swelling) and derived outcomes (area-under-the-curve) null hypotheses were tested with an analysis of covariance (ANCOVA) model. For comparisons using the specified ANCOVA models above, the least square mean for each treatment and the corresponding difference between least square means (EFM 5% patch - Placebo) with the p-value and 95% confidence interval were presented from the model.

Comparison groups	Placebo v Etofenamate 5% cutaneous patch

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least square mean
Point estimate	6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.8
upper limit	9.5
Variability estimate	Standard deviation

Secondary: AUC of pain on movement at Visit 5

End point title	AUC of pain on movement at Visit 5

End point description:

The area-under-the-curve (AUC) over time between baseline and the first 72 hours was calculated by means of the trapezoidal rule for POM measured by VAS.

End point type	Secondary

End point timeframe:

0 - 72 h after initiation of treatment

End point values	Etofenamate 5% cutaneous patch	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	78		
Units: mm * h				
arithmetic mean (standard deviation)	3851.2 (± 1266.5)	4655.5 (± 926.9)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

For quantitative efficacy outcomes assessed at the clinical trial sites (pain-on-movement, pain-at rest, ankle swelling) and derived outcomes (area-under-the-curve) null hypotheses were tested with an analysis of covariance (ANCOVA) model. For comparisons using the specified ANCOVA models above, the least square mean for each treatment and the corresponding difference between least square means (EFM 5% patch - Placebo) with the p-value and 95% confidence interval were presented from the model.

Comparison groups	Etofenamate 5% cutaneous patch v Placebo

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least square mean
Point estimate	879.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	677.3
upper limit	1081.7
Variability estimate	Standard deviation

Secondary: Circumference (ankle swelling)

End point title	Circumference (ankle swelling)

End point description:

The circumference measurements of ankle swelling as further secondary variable were carried out by "Figure-of-eight-method" comparing the injured ankle with the contralateral site.

End point type	Secondary

End point timeframe:

Visit 5 (72 h after initiation of treatment)

End point values	Etofenamate 5% cutaneous patch	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	78		
Units: cm				
arithmetic mean (standard deviation)	1.0 (± 0.9)	1.3 (± 1.0)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

For quantitative efficacy outcomes assessed at the clinical trial sites (pain-on-movement, pain-at rest, ankle swelling) and derived outcomes (area-under-the-curve) null hypotheses were tested with an analysis of covariance (ANCOVA) model. For comparisons using the specified ANCOVA models above, the least square mean for each treatment and the corresponding difference between least square means (EFM 5% patch - Placebo) with the p-value and 95% confidence interval were presented from the model.

Comparison groups	Etofenamate 5% cutaneous patch v Placebo

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Least square mean
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.4

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were documented from visit 1 (randomization, initiation of treatment) until visit 7 (day 7+1 of treatment)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Etofenamate 5% cutaneous patch
Reporting group description:	
Patients were treated with a cutaneous patch containing 5% etofenamate.	
Reporting group title	Placebo patch
Reporting group description:	
Patients were treated with a matching placebo cutaneous patch.	

Serious adverse events	Etofenamate 5% cutaneous patch	Placebo patch	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 78 (0.00%)	0 / 78 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Etofenamate 5% cutaneous patch	Placebo patch	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 78 (2.56%)	3 / 78 (3.85%)	
Nervous system disorders			
headache			
subjects affected / exposed	1 / 78 (1.28%)	1 / 78 (1.28%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	0 / 78 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Fatigue			

subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	1 / 78 (1.28%) 1	
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all)	1 / 78 (1.28%) 1	0 / 78 (0.00%) 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

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

None

Notes: