Clinical trial results:
Multi-centre, Double-blind, Randomised, Active- and Placebo-Controlled, Confirmatory Trial to Demonstrate Efficacy and Safety of Traumed® Gel in Patients having Acute Ankle Sprain

Summary

EudraCT number	2016-004792-50
Trial protocol	DE
Global end of trial date	25 March 2021
Results information	
Result version number	v1 (current)
This version publication date	04 October 2022
First version publication date	04 October 2022

Trial information

Trial identification	
Sponsor protocol code	C1502
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Biologische Heilmittel Heel GmbH
Sponsor organisation address	Dr.-Reckeweg-Str. 2 - 4, Baden-Baden, Germany, 76532
Public contact	Biologische Heilmittel Heel GmbH, Biologische Heilmittel Heel GmbH, +49 72215010, info@heel.com
Scientific contact	Biologische Heilmittel Heel GmbH, Biologische Heilmittel Heel GmbH, +49 72215010, info@heel.com

Notes:

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 March 2021
Global end of trial reached?	Yes
Global end of trial date	25 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to demonstrate the superior efficacy of Traumed gel versus Placebo gel in patients with acute unilateral ankle sprain.

Protection of trial subjects:

Rescue medication was allowed for randomised patients: Paracetamol (acetaminophen) 500 mg/tablets to be taken for pain relief when necessary; allowed maximum dose: 4 tablets or 2000 mg/d, and not >2 tablets at a time. Patients were not allowed to take Paracetamol within 8 h prior to Visit 2. For further visits the restriction was 24 h. Paracetamol was not allowed within 24 h prior to Visit 3, Visit 4 and Visit 5. A procedure for emergency unblinding was available.

Background therapy:

Supportive therapy was available for all patients: they received soft support (elastic bandage) on Day 1. All patients were trained how to use the elastic bandage and - if needed - the semi-rigid brace.
If Grade 1: soft support during entire trial, as required; if Grade 2: provision of semi-rigid removable brace on Day 7; if Grade 3: withdrawal from trial/further treatment at investigator´s discretion. There was strong recommendation to use arm crutches during entire trial and with special importance until Day 4. The patients were only to partly weight the sprained ankle when using crutches.
Use of RICE (simultaneous combination of all 4 elements Rest, Ice, Compression, and Elevation): restricted to time immediately after event, and before starting treatment with the investigational drug. After start of investigational treatment and during the entire course of the trial use of RICE was prohibited. The objective of RICE is to stop the injury-induced bleeding into the muscle tissue and thereby to minimise the extent of the injury.

Evidence for comparator:

Controlled trials of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) as Diclofenac and others in patients with ankle sprain showed that compared with Placebo, NSAIDs were associated with improved pain control and function, decreased swelling, and more rapid return to activity. Reviews of Diclofenac have consistently demonstrated its efficacy in reducing pain and inflammation in acute and chronic conditions compared with Placebo. Diclofenac is considered to be the gold standard in the treatment of joint sprains and other conditions. Topical Diclofenac is well tolerated and associated with fewer side-effects than other topical NSAIDs, mostly mild, easily resolved local skin irritation (Banning 2008 Expert Opinion on Pharmacotherapy, 9, 2921-9, Zacher et al. 2008 Current Medical Research and Opinion, 24, 925-50, Simon et al. 2009 Pain, 143, 238-45). A systematic review and meta-analysis of blinded, randomised, placebo-, vehicle- or active-controlled trials concluded that topical Diclofenac appears to be generally well tolerated for cutaneous use in acute and chronic musculoskeletal conditions (Taylor et al. 2011 Current Medical Research and Opinion, 27, 605-22). For these reasons, Diclofenac gel was chosen as a comparator for this trial.
In the other comparator arm a placebo gel was given.

Actual start date of recruitment	26 February 2018
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: 809
Worldwide total number of subjects	809
EEA total number of subjects	809

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)	786
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

28 German sites randomized 809 patients. Trial started in Q1/2018, planned recruitment period 12 months (mths). Recruitment interruption due to IMP expiry and resupply delay end of Dec 2019 till Feb 2020 and due to Sars-CoV-2 pandemic in spring 2020 (3 mths). Per Protocol Amendment v4.0 recruitment was extended by ~22 mths and ended on 18 Nov 2020.

Pre-assignment

Screening details:

809 patients (pts) with acute unilateral Grade (G) 1/2 sprain of the lateral ankle were enroled. G3 pts were not eligible. Following BfArM recommendations and EC agreement, 184 pts were excluded from main CTR population (625 pts) based on substantial amendment, final Blind Data Review Meeting decisions and individual patient listing in final SAP.

Period 1

Period 1 title	Full Analysis Set (FAS)
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:

Trial personnel, Sponsor, CRO/ other third-party vendors were blinded during the trial. Each site had a team member responsible exclusively for handling the investigational medicinal product (IMP) and soft support/ semi-rigid brace, and who was not involved in any other trial procedures related to the patient. For the entire trial duration, only the team member responsible exclusively for handling IMP was present at IMP gel applications/ removing/ replacing bandages/ braces.

Arms

Are arms mutually exclusive?	Yes
Arm title	Traumed gel

Arm description:

Patients randomised to treatment with Traumed gel 3 g of gel 3 times/day for 7 days; main Clinical Trial Report (CTR) population.
Full Analysis Set (FAS): n=622 treated patients; Traumed gel n=316 patients, Diclofenac gel n=151 patients; Placebo gel n=155 patients, based on a 2:1:1 randomisation ratio. FAS was to be used for intent-to-treat (ITT) analysis.

Arm type	Experimental
Investigational medicinal product name	Traumed
Investigational medicinal product code	
Other name	Tr14Gel
Pharmaceutical forms	Gel
Routes of administration	Topical, Topical use

Dosage and administration details:

3 g of gel three times daily for 7 days. Area of ankle should be sufficiently covered. First/last investigational medicinal product (IMP) was applied during Screening/ Baseline Visit (Day 1) and End of Treatment Visit (Day 7). All other IMP applications were to be made by the patient during the 7-day treatment period.

Arm title	Diclofenac 1% gel

Arm description:

Patients randomised to treatment with Diclofenac 1% gel, 3 g of gel 3 times/day for 7 days; main Clinical Trial Report (CTR) population.
Full Analysis Set (FAS): n=622 treated patients; Traumed gel n=316 patients, Diclofenac gel n=151 patients; Placebo gel n=155 patients, based on a 2:1:1 randomisation ratio. FAS was to be used for intent-to-treat (ITT) analysis.

Arm type	Active comparator

Investigational medicinal product name	Diclofenac
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical, Topical use

Dosage and administration details:

3 g of Diclofenac 1 % gel three times daily for 7 days. Area of ankle should be sufficiently covered. First/last investigational medicinal product (IMP) was applied during Screening/ Baseline Visit (Day 1) and End of Treatment Visit (Day 7). All other IMP applications were to be made by the patient during the 7-day treatment period.

Arm title	Placebo gel

Arm description:

Patients randomised to treatment with Placebo gel, 3 g of gel 3 times/day for 7 days; main Clinical Trial Report (CTR) population.
Full Analysis Set (FAS): n=622 treated patients; Traumed gel n=316 patients, Diclofenac gel n=151 patients; Placebo gel n=155 patients, based on a 2:1:1 randomisation ratio. FAS was to be used for intent-to-treat (ITT) analysis.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical, Topical use

Dosage and administration details:

3 g of gel three times daily for 7 days, to sufficiently cover the area of the ankle, applied by gentle rubbing. First/last investigational medicinal product (IMP) was applied during Screening/ Baseline Visit (Day 1) and End of Treatment Visit (Day 7). All other IMP applications were to be made by the patient during the 7-day treatment period.

Number of subjects in period 1[1]	Traumed gel	Diclofenac 1% gel	Placebo gel
Started	316	151	155
Completed	314	146	155
Not completed	2	5	0
Inclusion violation	-	1	-
Compliance < 80%	-	2	-
Premature discontinuation	2	-	-
Visit deviation	-	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Initially, N=809 patients (pts) were enroled. Following BfArM recommendations and in agreement with the Ethics Committee, 184 pts were excluded from main CTR population (based on substantial amendment, final Blind Data Review Meeting decisions and individual listing in final Statistical Analysis Plan). The remaining n=625 pts constitute the main Clinical Trial Report and Safety population.

Period 2

Period 2 title	Per Protocol (PP) analysis set
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Trial personnel, Sponsor, CRO/ other third-party vendors were blinded during the trial. Each site had a team member responsible exclusively for handling the investigational medicinal product (IMP) and soft support/ semi-rigid brace, and who was not involved in any other trial procedures related to the patient. For the entire trial duration, only the team member responsible exclusively for handling IMP was present at IMP gel applications/ removing/ replacing bandages/ braces.

Arms

Are arms mutually exclusive?	Yes
Arm title	Traumed gel

Arm description:

Patients randomised to treatment with Traumed gel 3 g of gel 3 times/day for 7 days; main Clinical Trial Report (CTR) population.
Per Protocol (PP) analysis set: n=615 treated patients; Traumed gel n=314 patients, Diclofenac gel n=146 patients; Placebo gel n=155 patients, based on a 2:1:1 randomisation ratio.

Arm type	Experimental
Investigational medicinal product name	Traumed
Investigational medicinal product code	
Other name	Tr14Gel
Pharmaceutical forms	Gel
Routes of administration	Topical, Topical use

Dosage and administration details:

3 g of gel three times daily for 7 days. Area of ankle should be sufficiently covered. First/last investigational medicinal product (IMP) was applied during Screening/ Baseline Visit (Day 1) and End of Treatment Visit (Day 7). All other IMP applications were to be made by the patient during the 7-day treatment period.

Arm title	Diclofenac 1% gel

Arm description:

Patients randomised to treatment with Diclofenac 1% gel, 3 g of gel 3 times/day for 7 days; main Clinical Trial Report (CTR) population.
Per Protocol (PP) analysis set: n=615 treated patients; Traumed gel n=314 patients, Diclofenac gel n=146 patients; Placebo gel n=155 patients, based on a 2:1:1 randomisation ratio.

Arm type	Active comparator
Investigational medicinal product name	Diclofenac
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical, Topical use

Dosage and administration details:

3 g of Diclofenac 1 % gel three times daily for 7 days. Area of ankle should be sufficiently covered. First/last investigational medicinal product (IMP) was applied during Screening/ Baseline Visit (Day 1) and End of Treatment Visit (Day 7). All other IMP applications were to be made by the patient during the 7-day treatment period.

Arm title	Placebo gel

Arm description:

Patients randomised to treatment with Placebo gel, 3 g of gel 3 times/day for 7 days; main Clinical Trial Report (CTR) population.
Per Protocol (PP) analysis set: n=615 treated patients; Traumed gel n=314 patients, Diclofenac gel n=146 patients; Placebo gel n=155 patients, based on a 2:1:1 randomisation ratio.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical, Topical use

Dosage and administration details:

3 g of gel three times daily for 7 days, to sufficiently cover the area of the ankle, applied by gentle rubbing. First/last investigational medicinal product (IMP) was applied during Screening/ Baseline Visit (Day 1) and End of Treatment Visit (Day 7). All other IMP applications were to be made by the patient during the 7-day treatment period.

Number of subjects in period 2	Traumed gel	Diclofenac 1% gel	Placebo gel
Started	314	146	155
Completed	314	146	155

Baseline characteristics

Reporting groups	
Reporting group title	Traumed gel
Reporting group description:	
Patients randomised to treatment with Traumed gel 3 g of gel 3 times/day for 7 days; main Clinical Trial Report (CTR) population. Full Analysis Set (FAS): n=622 treated patients; Traumed gel n=316 patients, Diclofenac gel n=151 patients; Placebo gel n=155 patients, based on a 2:1:1 randomisation ratio. FAS was to be used for intent-to-treat (ITT) analysis.	
Reporting group title	Diclofenac 1% gel
Reporting group description:	
Patients randomised to treatment with Diclofenac 1% gel, 3 g of gel 3 times/day for 7 days; main Clinical Trial Report (CTR) population. Full Analysis Set (FAS): n=622 treated patients; Traumed gel n=316 patients, Diclofenac gel n=151 patients; Placebo gel n=155 patients, based on a 2:1:1 randomisation ratio. FAS was to be used for intent-to-treat (ITT) analysis.	
Reporting group title	Placebo gel
Reporting group description:	
Patients randomised to treatment with Placebo gel, 3 g of gel 3 times/day for 7 days; main Clinical Trial Report (CTR) population. Full Analysis Set (FAS): n=622 treated patients; Traumed gel n=316 patients, Diclofenac gel n=151 patients; Placebo gel n=155 patients, based on a 2:1:1 randomisation ratio. FAS was to be used for intent-to-treat (ITT) analysis.	

Reporting group values	Traumed gel	Diclofenac 1% gel	Placebo gel
Number of subjects	316	151	155
Age categorical Units: Subjects			
Adults (18-64 years)	305	147	152
From 65-84 years	11	4	3
Age continuous Units: years			
arithmetic mean	35.2	34.7	36.0
standard deviation	± 14.11	± 13.53	± 13.66
Gender categorical Units: Subjects			
Female	156	64	68
Male	160	87	87
Ethnic origin Units: Subjects			
Caucasian	305	149	152
Black	3	0	2
Asian	1	0	0
Other	7	2	1
Injury Grading Units: Subjects			
Grade 1	216	109	103
Grade 2	100	42	52
Grade 3	0	0	0

Body-Mass-Index (BMI) Units: kg/m^2			
arithmetic mean	26.2	24.7	26.2
standard deviation	± 4.80	± 4.08	± 4.63
Efficacy - VAS pain score on Passive Movement (VASPM) Units: mm			
arithmetic mean	74.9	74.9	75.5
standard deviation	± 10.97	± 11.41	± 11.36
Efficacy - VAS pain score at Rest (VASRS) Units: mm			
arithmetic mean	39.4	37.0	39.7
standard deviation	± 24.65	± 23.87	± 23.88
Efficacy - Foot and Ankle Ability Measure - Activities of Daily Living (FAAM)			
The FAAM-ADL subscale is part of the Foot and Ankle Ability Measure (FAAM) questionnaire and consists of 21 single items assessing Activities of Daily Living as standing, walking, going up stairs, etc. eCRF instruction was: "Please answer each question with the response that most closely describes your condition during the past week", with minimum: 0 and maximum: 100.			
Units: Score			
arithmetic mean	51.4	50.6	49.7
standard deviation	± 17.36	± 18.6	± 18.01

Reporting group values	Total		
Number of subjects	622		
Age categorical Units: Subjects			
Adults (18-64 years)	604		
From 65-84 years	18		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	288		
Male	334		
Ethnic origin Units: Subjects			
Caucasian	606		
Black	5		
Asian	1		
Other	10		
Injury Grading Units: Subjects			
Grade 1	428		
Grade 2	194		
Grade 3	0		
Body-Mass-Index (BMI) Units: kg/m^2			
arithmetic mean			

standard deviation	-		
Efficacy - VAS pain score on Passive Movement (VASPM) Units: mm arithmetic mean standard deviation	- -		
Efficacy - VAS pain score at Rest (VASRS) Units: mm arithmetic mean standard deviation	- -		
Efficacy - Foot and Ankle Ability Measure - Activities of Daily Living (FAAM)			
The FAAM-ADL subscale is part of the Foot and Ankle Ability Measure (FAAM) questionnaire and consists of 21 single items assessing Activities of Daily Living as standing, walking, going up stairs, etc. eCRF instruction was: "Please answer each question with the response that most closely describes your condition during the past week", with minimum: 0 and maximum: 100.			
Units: Score arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Traumed gel

Reporting group description:

Patients randomised to treatment with Traumed gel 3 g of gel 3 times/day for 7 days; main Clinical Trial Report (CTR) population.
Full Analysis Set (FAS): n=622 treated patients; Traumed gel n=316 patients, Diclofenac gel n=151 patients; Placebo gel n=155 patients, based on a 2:1:1 randomisation ratio. FAS was to be used for intent-to-treat (ITT) analysis.

Reporting group title	Diclofenac 1% gel

Reporting group description:

Patients randomised to treatment with Diclofenac 1% gel, 3 g of gel 3 times/day for 7 days; main Clinical Trial Report (CTR) population.
Full Analysis Set (FAS): n=622 treated patients; Traumed gel n=316 patients, Diclofenac gel n=151 patients; Placebo gel n=155 patients, based on a 2:1:1 randomisation ratio. FAS was to be used for intent-to-treat (ITT) analysis.

Reporting group title	Placebo gel

Reporting group description:

Patients randomised to treatment with Placebo gel, 3 g of gel 3 times/day for 7 days; main Clinical Trial Report (CTR) population.
Full Analysis Set (FAS): n=622 treated patients; Traumed gel n=316 patients, Diclofenac gel n=151 patients; Placebo gel n=155 patients, based on a 2:1:1 randomisation ratio. FAS was to be used for intent-to-treat (ITT) analysis.

Reporting group title	Traumed gel

Reporting group description:

Patients randomised to treatment with Traumed gel 3 g of gel 3 times/day for 7 days; main Clinical Trial Report (CTR) population.
Per Protocol (PP) analysis set: n=615 treated patients; Traumed gel n=314 patients, Diclofenac gel n=146 patients; Placebo gel n=155 patients, based on a 2:1:1 randomisation ratio.

Reporting group title	Diclofenac 1% gel

Reporting group description:

Patients randomised to treatment with Diclofenac 1% gel, 3 g of gel 3 times/day for 7 days; main Clinical Trial Report (CTR) population.
Per Protocol (PP) analysis set: n=615 treated patients; Traumed gel n=314 patients, Diclofenac gel n=146 patients; Placebo gel n=155 patients, based on a 2:1:1 randomisation ratio.

Reporting group title	Placebo gel

Reporting group description:

Patients randomised to treatment with Placebo gel, 3 g of gel 3 times/day for 7 days; main Clinical Trial Report (CTR) population.
Per Protocol (PP) analysis set: n=615 treated patients; Traumed gel n=314 patients, Diclofenac gel n=146 patients; Placebo gel n=155 patients, based on a 2:1:1 randomisation ratio.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety population matches the main Cllinical Trial Report population of n=625 patients randomized 2:1:1 to Traumed gel n=318, Diclofenac 1% gel n=152 and Placebo n=155. There were no Safety exclusions from the randomized population. There were n=3 Full Analysis Set (FAS) exclusions from the Safety population due to no follow-up efficacy data, leaving a FAS of n=622.

Primary: Area Under the Curve (AUC) for pain on passive movement in Visual Analog Scale (VAS) from Baseline to Day 4

End point title	Area Under the Curve (AUC) for pain on passive movement in Visual Analog Scale (VAS) from Baseline to Day 4

End point description:

Ankle pain measurement by 100 mm VAS with start 'no pain' (0 mm) and end 'most severe imaginable pain' patients may imagine in relation to their ankle sprain (100 mm). After 5 min rest, patients assessed their pain on a VAS scale (2nd efficacy assessment). Still at rest investigators performed

flexion on the injured ankle: then patients assessed their pain on a VAS scale (1st efficacy assessment). Pain to be assessed: pain on passive movement. Endpoint data were calculated based on actual time of measurement. Missing values were replaced by Last Observation Carried Forward (LOCF). Statistical analysis based on Full Analysis Set n=622 (1st set for evaluation of superiority of Traumed versus (v) Placebo gel, 2nd set for evaluation of non-inferiority of Traumed v Diclofenac gel), and on the Per Protocol analysis set n=615 (1st set for evaluation of non-inferiority of Traumed v Diclofenac gel, 2nd set for evaluation of superiority of Traumed v Placebo gel). Absolute values are shown.

End point type	Primary

End point timeframe:

Baseline (Visit 1) to Day 4 (Visit 3)

End point values	Traumed gel	Diclofenac 1% gel	Placebo gel	Traumed gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	316[1]	151[2]	155[3]	314[4]
Units: mm				
median (full range (min-max))				
Day 4 (Visit 3)	187.88 (51.46 to 370.72)	197.16 (39.94 to 366.54)	200.75 (86.08 to 374.43)	187.50 (51.46 to 370.73)

Notes:

[1] - Full Analysis Set n=622

[2] - Full Analysis Set n=622

[3] - Full Analysis Set n=622

[4] - Per Protocol analysis set n=615

End point values	Diclofenac 1% gel			
Subject group type	Reporting group			
Number of subjects analysed	146[5]			
Units: mm				
median (full range (min-max))				
Day 4 (Visit 3)	197.19 (76.74 to 366.54)			

Notes:

[5] - Per Protocol analysis set n=615

Statistical analyses

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 4 (Visit 3)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.0205
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D4V3

Statistical analysis description:

Time point: Day 4 (Visit 3) - D4V3
Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.0138
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5698
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5163
upper limit	0.6233

Notes:

[6] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 4 (Visit 3)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4812
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D4V3

Statistical analysis description:

Time point: Day 4 (Visit 3) - D4V3
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	= 0.3804
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5254
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4698
upper limit	0.581

Notes:

[7] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Primary: Area Under the Curve (AUC) for pain on passive movement in Visual Analog Scale (VAS) from Baseline to Day 7

End point title	Area Under the Curve (AUC) for pain on passive movement in Visual Analog Scale (VAS) from Baseline to Day 7

End point description:

Ankle pain measurement by 100 mm VAS with start 'no pain' (0 mm) and end 'most severe imaginable pain' patients may imagine in relation to their ankle sprain (100 mm). After 5 min rest, patients assessed their pain on a VAS scale (2nd efficacy assessment). Still at rest investigators performed flexion on the injured ankle: then patients assessed their pain on a VAS scale (1st efficacy assessment). Pain to be assessed: pain on passive movement. Endpoint data were calculated based on actual time of measurement. Missing values were replaced by Last Observation Carried Forward (LOCF). Statistical analysis based on Full Analysis Set n=622 (1st set for evaluation of superiority of Traumed versus (v) Placebo gel, 2nd set for evaluation of non-inferiority of Traumed v Diclofenac gel), and on the Per Protocol analysis set n=615 (1st set for evaluation of non-inferiority of Traumed v Diclofenac gel, 2nd set for evaluation of superiority of Traumed v Placebo gel). Absolute values are shown.

End point type	Primary

End point timeframe:

Baseline (Visit 1) to Day 7 (Visit 4, End of Treatment)

End point values	Traumed gel	Diclofenac 1% gel	Placebo gel	Traumed gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	316[8]	151[9]	155[10]	314[11]
Units: mm				
median (full range (min-max))				
Day 7 (Visit 4)	294.14 (63.46 to 592.47)	327.68 (53.93 to 637.79)	353.42 (101.28 to 620.07)	293.85 (63.46 to 592.47)

Notes:

[8] - Full Analysis Set n=622

[9] - Full Analysis Set n=622

[10] - Full Analysis Set n=622

[11] - Per Protocol analysis set n=615

End point values	Diclofenac 1% gel			
Subject group type	Reporting group			
Number of subjects analysed	146[12]			
Units: mm				
median (full range (min-max))				
Day 7 (Visit 4)	327.93 (94.76 to 637.79)			

Notes:

[12] - Per Protocol analysis set n=615

Statistical analyses

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 7 (Visit 4)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D7V4

Statistical analysis description:

Time point: Day 7 (Visit 4) - D7V4
Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.6387
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5862
upper limit	0.6911

Notes:

[13] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 7 (Visit 4)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0034
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D7V4

Statistical analysis description:

Time point: Day 7 (Visit 4) - D7V4
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel

Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
P-value	= 0.0017
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.591
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.537
upper limit	0.645

Notes:

[14] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Secondary: Area Under the Curve (AUC) for pain at rest in Visual Analog Scale (VAS) from Baseline to Day 4

End point title	Area Under the Curve (AUC) for pain at rest in Visual Analog Scale (VAS) from Baseline to Day 4

End point description:

Ankle pain was measured using a 100 mm VAS starting with 'no pain' (0 mm) and ending with 'most severe imaginable pain' the patient may have imagined in relation to his/her ankle sprain (100 mm). The patients were asked after 5 minutes rest to assess their pain themselves on a VAS scale. AUC for pain at rest in VAS from baseline to Day 4 (Visit 3) and Day 7 (Visit 4) was calculated based on actual time of pain measurement. Missing values were replaced by Last Observation Carried Forward (LOCF). Statistical analysis based on Full Analysis Set n=622 (1st set for evaluation of superiority of Traumed gel versus (v) Placebo gel, 2nd set for evaluation of non-inferiority of Traumed gel v Diclofenac gel), and on the Per Protocol analysis set n=615 (1st set for evaluation of non-inferiority of Traumed gel v Diclofenac gel, 2nd set for evaluation of superiority of Traumed gel v Placebo gel). Absolute values are shown.

End point type	Secondary

End point timeframe:

Baseline (Visit 1) to Day 4 (Visit 3)

End point values	Traumed gel	Diclofenac 1% gel	Placebo gel	Traumed gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	316[15]	151[16]	155[17]	314[18]
Units: mm				
median (full range (min-max))				
Day 4 (Visit 3)	65.90 (2.48 to 305.50)	58.59 (6.67 to 272.50)	73.36 (2.49 to 259.22)	65.38 (2.48 to 305.50)

Notes:

[15] - Full Analysis Set n=622

[16] - Full Analysis Set n=622

[17] - Full Analysis Set n=622

[18] - Per Protocol analysis set n=615

End point values	Diclofenac 1% gel			
Subject group type	Reporting group			
Number of subjects analysed	146[19]			

Units: mm				
median (full range (min-max))				
Day 4 (Visit 3)	58.40 (6.67 to 272.50)			

Notes:

[19] - Per Protocol analysis set n=615

Statistical analyses

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 4 (Visit 3)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7015
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D4V3

Statistical analysis description:

Time point: Day 4 (Visit 3) - D4V3
Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.219
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5349
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4808
upper limit	0.589

Notes:

[20] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 4 (Visit 3)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel

Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1189
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D4V3

Statistical analysis description:

Time point: Day 4 (Visit 3) - D4V3
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
P-value	= 0.4074
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.476
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.419
upper limit	0.533

Notes:

[21] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Secondary: Area Under the Curve (AUC) for pain on passive movement in Visual Analog Scale (VAS) from Baseline to Day 2, and Final Visit

End point title	Area Under the Curve (AUC) for pain on passive movement in Visual Analog Scale (VAS) from Baseline to Day 2, and Final Visit

End point description:

Ankle pain measurement by 100 mm VAS with start 'no pain' (0 mm) and end 'most severe imaginable pain' patients may imagine in relation to their ankle sprain (100 mm). After 5 min rest, patients assessed their pain on a VAS scale (2nd efficacy assessment). Still at rest investigators performed flexion on the injured ankle: then patients assessed their pain on a VAS scale (1st efficacy assessment). Pain to be assessed: pain on passive movement. Endpoint data were calculated based on actual time of measurement. Missing values were replaced by Last Observation Carried Forward (LOCF). Statistical analysis based on Full Analysis Set n=622 (1st set for evaluation of superiority of Traumed versus (v) Placebo gel, 2nd set for evaluation of non-inferiority of Traumed v Diclofenac gel), and on the Per Protocol analysis set n=615 (1st set for evaluation of non-inferiority of Traumed v Diclofenac gel, 2nd set for evaluation of superiority of Traumed v Placebo gel). Absolute values are shown.

End point type	Secondary

End point timeframe:

Baseline (Visit 1) to Day 2 (Visit 2) and Visit 5 (Day 14, Final Visit)

End point values	Traumed gel	Diclofenac 1% gel	Placebo gel	Traumed gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	316[22]	151[23]	155[24]	314[25]
Units: mm				
median (full range (min-max))				
Day 2 (Visit 2)	69.00 (30.40 to 114.40)	70.49 (24.92 to 150.78)	70.51 (39.97 to 97.51)	68.88 (30.40 to 114.40)
Day 14 (Visit 5) Final Visit	394.65 (66.96 to 1126.39)	503.36 (57.43 to 1266.54)	577.00 (101.28 to 1050.77)	394.37 (66.96 to 1126.39)

Notes:

[22] - Full Analysis Set n=622

[23] - Full Analysis Set n=622

[24] - Full Analysis Set n=622

[25] - Per Protocol analysis set n=615

End point values	Diclofenac 1% gel			
Subject group type	Reporting group			
Number of subjects analysed	146[26]			
Units: mm				
median (full range (min-max))				
Day 2 (Visit 2)	70.58 (34.71 to 98.85)			
Day 14 (Visit 5) Final Visit	505.39 (98.76 to 1266.54)			

Notes:

[26] - Per Protocol analysis set n=615

Statistical analyses

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 2 (Visit 2)
Statistical analysis description:	
Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.	
Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2962
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D2V2
Statistical analysis description:	
Time point: Day 2 (Visit 2) - D2V2 Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622. CI, Confidence interval	
Comparison groups	Traumed gel v Placebo gel

Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.2361
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5336
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4792
upper limit	0.588

Notes:

[27] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 14 (Visit 5)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D14

Statistical analysis description:

Time point: Day 14 (Visit 5) - D14V5
Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.6803
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6282
upper limit	0.7325

Notes:

[28] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 2 (Visit 2)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6359
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D2V2

Statistical analysis description:

Time point: Day 2 (Visit 2) - D2V2
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[29]
P-value	= 0.7227
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5103
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.454
upper limit	0.5665

Notes:

[29] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 14 (Visit 5)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0001
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D14

Statistical analysis description:

Time point: Day 14 (Visit 5) - D14V5
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel

Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[30]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.6234
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5701
upper limit	0.6768

Notes:

[30] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Secondary: Area Under the Curve (AUC) for pain at rest in Visual Analog Scale (VAS) from Baseline to Day 2, 7 and Final Visit

End point title	Area Under the Curve (AUC) for pain at rest in Visual Analog Scale (VAS) from Baseline to Day 2, 7 and Final Visit

End point description:

Ankle pain was measured using a 100 mm VAS starting with 'no pain' (0 mm) and ending with 'most severe imaginable pain' the patient may have imagined in relation to his/her ankle sprain (100 mm). The patients were asked after 5 minutes rest to assess their pain themselves on a VAS scale. AUC for pain at rest in VAS from baseline to Day 4 (Visit 3) and Day 7 (Visit 4) was calculated based on actual time of pain measurement. Missing values were replaced by Last Observation Carried Forward (LOCF). Statistical analysis based on Full Analysis Set n=622 (1st set for evaluation of superiority of Traumed gel versus (v) Placebo gel, 2nd set for evaluation of non-inferiority of Traumed gel v Diclofenac gel), and on the Per Protocol analysis set n=615 (1st set for evaluation of non-inferiority of Traumed gel v Diclofenac gel, 2nd set for evaluation of superiority of Traumed gel v Placebo gel). Absolute values are shown.

End point type	Secondary

End point timeframe:

Baseline (Visit 1) to Day 2 (Visit 2), Day 7 (Visit 4, End of Treatment) and Day 14 (Visit 5, Final Visit)

End point values	Traumed gel	Diclofenac 1% gel	Placebo gel	Traumed gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	316[31]	151[32]	155[33]	314[34]
Units: mm				
median (full range (min-max))				
Day 2 (Visit 2)	28.0 (0 to 107.4)	25.4 (2.6 to 86.5)	31.4 (0 to 91.5)	27.4 (0.0 to 107.4)
Day 7 (Visit 4)	90.3 (2.5 to 570.5)	91.6 (11.5 to 435.5)	109.8 (2.5 to 504.3)	90.1 (2.5 to 570.5)
Day 14 (Visit 5)	116.1 (2.5 to 895.5)	130.4 (12.5 to 872.0)	159.7 (2.5 to 896.5)	113.4 (2.5 to 895.5)

Notes:

[31] - Full Analysis Set n=622

[32] - Full Analysis Set n=622

[33] - Full Analysis Set n=622

[34] - Per Protocol analysis set n=615

End point values	Diclofenac 1% gel			
Subject group type	Reporting group			
Number of subjects analysed	146[35]			
Units: mm				
median (full range (min-max))				
Day 2 (Visit 2)	24.9 (2.6 to 86.5)			
Day 7 (Visit 4)	88.4 (11.5 to 435.5)			
Day 14 (Visit 5)	128.9 (12.5 to 872.0)			

Notes:

[35] - Per Protocol analysis set n=615

Statistical analyses

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 2 (Visit 2)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9383
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D2V2

Statistical analysis description:

Time point: Day 2 (Visit 2) - D2V2
Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.584
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5155
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4609
upper limit	0.5702

Notes:

[36] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 7 (Visit 4)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2219
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D7V4

Statistical analysis description:

Time point: Day 7 (Visit 4) - D7V4
Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.0166
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5679
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5148
upper limit	0.6211

Notes:

[37] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 14 (Visit 5)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0816
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D14

Statistical analysis description:

Time point: Day 14 (Visit 5) - D14V5
Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel

Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.0005
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5991
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5467
upper limit	0.6514

Notes:

[38] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 2 (Visit 2)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1074
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D2V2

Statistical analysis description:

Time point: Day 2 (Visit 2) - D2V2
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[39]
P-value	= 0.3017
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.4701
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4128
upper limit	0.5274

Notes:

[39] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 7 (Visit 4)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4099
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D7V4

Statistical analysis description:

Time point: Day 7 (Visit 4) - D7V4
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[40]
P-value	= 0.9441
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.502
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.446
upper limit	0.5581

Notes:

[40] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 14 (Visit 5)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7509
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D14

Statistical analysis description:

Time point: Day 14 (Visit 5) - D14V5
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel

Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[41]
P-value	= 0.3431
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5275
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4723
upper limit	0.5827

Notes:

[41] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Secondary: Change from Baseline of pain on passive movement in Visual Analog Scale (VAS) to Day 4, Day 7 and Final Visit

End point title	Change from Baseline of pain on passive movement in Visual Analog Scale (VAS) to Day 4, Day 7 and Final Visit

End point description:

Ankle pain measurement by 100 mm VAS with start 'no pain' (0 mm) and end 'most severe imaginable pain' patients may imagine in relation to their ankle sprain (100 mm). After 5 min rest, patients assessed their pain on a VAS scale (2nd efficacy assessment). Still at rest investigators performed flexion on the injured ankle: then patients assessed their pain on a VAS scale (1st efficacy assessment). Pain to be assessed: pain on passive movement. Missing values were replaced by Last Observation Carried Forward (LOCF). Statistical analysis based on Full Analysis Set n=622 (1st set for evaluation of superiority of Traumed versus (v) Placebo gel, 2nd set for evaluation of non-inferiority of Traumed v Diclofenac gel), and on the Per Protocol analysis set n=615 (1st set for evaluation of non-inferiority of Traumed v Diclofenac gel, 2nd set for evaluation of superiority of Traumed v Placebo gel). Change from Baseline on the VAS pain on passive movement scale at time of measurement is shown.

End point type	Secondary

End point timeframe:

Baseline (Visit 1) to Day 4 (Visit 3), Day 7 (Visit 4, End of Treatment) and Day 14 (Visit 5, Final Visit)

End point values	Traumed gel	Diclofenac 1% gel	Placebo gel	Traumed gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	316[42]	151[43]	155[44]	314[45]
Units: mm				
median (full range (min-max))				
Day 4 (Visit 3)	-30.0 (-94.0 to 10.0)	-21.0 (-92.0 to 7.0)	-20.0 (-78.0 to 17.0)	-30.0 (-94.0 to 10.0)
Day 7 (Visit 4)	-49.5 (-94.0 to 9.0)	-40.0 (-92.0 to 2.0)	-35.0 (-92.0 to 11.0)	-50.0 (-94.0 to -3.0)
Day 14 (Visit 5)	-65.5 (-98.0 to 9.0)	-60.0 (-97.0 to 5.0)	-57.0 (-94.0 to -1.0)	-66.5 (-98.0 to 4.0)

Notes:

[42] - Full Analysis Set n=622

[43] - Full Analysis Set n=622

[44] - Full Analysis Set n=622

[45] - Per Protocol analysis set n=615

End point values	Diclofenac 1% gel			
Subject group type	Reporting group			
Number of subjects analysed	146[46]			
Units: mm				
median (full range (min-max))				
Day 4 (Visit 3)	-21.0 (-92.0 to 7.0)			
Day 7 (Visit 4)	-40.0 (-92.0 to 2.0)			
Day 14 (Visit 5)	-61.0 (-97.0 to 5.0)			

Notes:

[46] - Per Protocol analysis set n=615

Statistical analyses

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 4 (Visit 3)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D4V3

Statistical analysis description:

Time point: Day 4 (Visit 3) - D4V3
Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.6468
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5945
upper limit	0.6992

Notes:

[47] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 7 (Visit 4)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D7V4

Statistical analysis description:

Time point: Day 7 (Visit 4) - D7V4
Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.6629
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6107
upper limit	0.715

Notes:

[48] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 14 (Visit 5)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D14

Statistical analysis description:

Time point: Day 14 (Visit 5) - D14V5
Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel

Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.6403
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5878
upper limit	0.6928

Notes:

[49] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 4 (Visit 3)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0019
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D4V3

Statistical analysis description:

Time point: Day 4 (Visit 3) - D4V3
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[50]
P-value	= 0.0005
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.6001
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5459
upper limit	0.6542

Notes:

[50] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 7 (Visit 4)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D7V4

Statistical analysis description:

Time point: Day 7 (Visit 4) - D7V4
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[51]
P-value	= 0.0002
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.6072
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5533
upper limit	0.6611

Notes:

[51] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 14 (Visit 5)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0006
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D14

Statistical analysis description:

Time point: Day 14 (Visit 5) - D14V5
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel

Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[52]
P-value	= 0.0094
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5752
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5202
upper limit	0.6302

Notes:

[52] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Secondary: Change from Baseline of pain at rest in Visual Analog Scale (VAS) to Day 4, 7 and Final Visit

End point title	Change from Baseline of pain at rest in Visual Analog Scale (VAS) to Day 4, 7 and Final Visit

End point description:

Ankle pain was measured using a 100 mm VAS starting with 'no pain' (0 mm) and ending with 'most severe imaginable pain' the patient may have imagined in relation to his/her ankle sprain (100 mm). The patients were asked after 5 minutes rest to assess their pain themselves on a VAS scale. Missing values were replaced by Last Observation Carried Forward (LOCF). Statistical analysis based on Full Analysis Set n=622 (1st set for evaluation of superiority of Traumed gel versus (v) Placebo gel, 2nd set for evaluation of non-inferiority of Traumed gel v Diclofenac gel), and on the Per Protocol (PP) analysis set n=615 (1st set for evaluation of non-inferiority of Traumed gel v Diclofenac gel, 2nd set for evaluation of superiority of Traumed gel v Placebo gel. Change from Baseline on the VAS pain at rest scale at time of measurement is shown.

End point type	Secondary

End point timeframe:

Baseline (Visit 1) to Day 4 (Visit 3), Day 7 (Visit 4, End of Treatment) and Day 14 (Visit 5; Final Visit)

End point values	Traumed gel	Diclofenac 1% gel	Placebo gel	Traumed gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	316[53]	151[54]	155[55]	314[56]
Units: mm				
median (full range (min-max))				
Day 4 (Visit 3)	-14.0 (-95.0 to 23.0)	-11.0 (-87.0 to 10.0)	-10.0 (-75.0 to 17.0)	-14.0 (-95.0 to 23.0)
Day 7 (Visit 4)	-21.0 (-95.0 to 7.0)	-17.0 (-87.0 to 3.0)	-20.0 (-77.0 to 15.0)	-21.0 (-95.0 to 7.0)
Day 14 (Visit 5)	-29.0 (-95.0 to 5.0)	-24.0 (-88.0 to 6.0)	-27.0 (-95.0 to 21.0)	-29.0 (-95.0 to 0.0)

Notes:

[53] - Full Analysis Set n=622

[54] - Full Analysis Set n=622

[55] - Full Analysis Set n=622

[56] - Per Protocol analysis set n=615

End point values	Diclofenac 1% gel			

Subject group type	Reporting group			
Number of subjects analysed	146[57]			
Units: mm				
median (full range (min-max))				
Day 4 (Visit 3)	-11.0 (-87.0 to 10.0)			
Day 7 (Visit 4)	-15.5 (-87.0 to 3.0)			
Day 14 (Visit 5)	-22.5 (-88.0 to 6.0)			

Notes:

[57] - Per Protocol analysis set n=615

Statistical analyses

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 4 (Visit 3)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0438
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D4V3

Statistical analysis description:

Time point: Day 4 (Visit 3) - D4V3
Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[58]
P-value	= 0.0273
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5625
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5083
upper limit	0.6168

Notes:

[58] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 7 (Visit 4)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.

Comparison groups	Traumed gel v Placebo gel

Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0807
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D7V4

Statistical analysis description:

Time point: Day 7 (Visit 4) - D7V4
Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[59]
P-value	= 0.0663
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.552
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4975
upper limit	0.6066

Notes:

[59] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 14 (Visit 5)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1675
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D14

Statistical analysis description:

Time point: Day 14 (Visit 5) - D14V5
Hypothesis no. 1 (superiority) is based on the Full Analysis Set (FAS); FAS n=622.
CI, confidence interval

Comparison groups	Placebo gel v Traumed gel

Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[60]
P-value	= 0.2805
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5306
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4758
upper limit	0.5853

Notes:

[60] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 4 (Visit 3)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1389
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D4V3

Statistical analysis description:

Time point: Day 4 (Visit 3) - D4V3
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[61]
P-value	= 0.0798
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5507
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4954
upper limit	0.606

Notes:

[61] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 7 (Visit 4)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0346
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D7V4

Statistical analysis description:

Time point: Day 7 (Visit 4) - D7V4
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[62]
P-value	= 0.0184
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5683
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5132
upper limit	0.6233

Notes:

[62] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 14 (Visit 5)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0915
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D14

Statistical analysis description:

Time point: Day 14 (Visit 5) - D14V5
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel

Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[63]
P-value	= 0.1561
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5411
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4857
upper limit	0.5965

Notes:

[63] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Secondary: Change from Baseline to Day 2, 4, 7 and Final Visit in the Foot and Ankle Ability Measure (FAAM) Activities of Daily Living (ADL) subscale

End point title	Change from Baseline to Day 2, 4, 7 and Final Visit in the Foot and Ankle Ability Measure (FAAM) Activities of Daily Living (ADL) subscale

End point description:

The FAAM is a validated questionnaire, developed to meet the need for a self-reported evaluative instrument that assesses physical function of individuals with musculoskeletal disorders of the leg, foot, and ankle. It is well-established and widely used. The FAAM-ADL subscale is part of the FAAM questionnaire and consists of 21 single items assessing Activities of Daily Living as standing, walking, going up stairs, etc. Possible responses for items: 'no'/ 'slight'/ 'moderate'/ 'extreme difficulty'/ 'unable to do' and 'not applicable'. The response to each item on the FAAM-ADL subscale was recorded from 4 ‘no difficulty’ and 0 ‘unable to do’. For this analysis scores were transformed: a lower score represents a higher level of physical function (normalised of mean, %max neg. score). Missing values are replaced by Last Observation Carried Forward (LOCF). Analysis based on Full Analysis Set n=622 and Per Protocol analysis set n=615. Change from Baseline at time of measurement is shown.

End point type	Secondary

End point timeframe:

Baseline (Visit 1) to Day 2 (Visit 2), Day 4 (Visit 3), Day 7 (Visit 4, End of Treatment) and Day 14 (Visit 5, Final Visit)

End point values	Traumed gel	Diclofenac 1% gel	Placebo gel	Traumed gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	316[64]	151[65]	155[66]	314[67]
Units: Score				
median (full range (min-max))				
Day 2 (Visit 2)	-3.6 (-33.3 to 59.5)	-2.4 (-47.6 to 47.6)	-0.6 (-36.9 to 61.9)	-3.6 (-33.3 to 59.5)
Day 4 (Visit 3)	-17.9 (-61.9 to 36.9)	-15.2 (-69.1 to 35.7)	-11.2 (-51.2 to 56.0)	-17.7 (-61.9 to 36.9)
Day 7 (Visit 4)	-29.1 (-78.4 to 23.2)	-26.2 (-85.7 to 22.6)	-22.6 (-64.8 to 46.4)	-29.1 (-78.4 to 23.2)
Day 14 (Visit 5)	-42.7 (-85.7 to 12.4)	-39.7 (-95.2 to 7.1)	-35.7 (-86.2 to 36.9)	-42.8 (-85.7 to 12.4)

Notes:

[64] - Full Analysis Set n=622

[65] - Full Analysis Set n=622

[66] - Full Analysis Set n=622

[67] - Per Protocol analysis set n=615

End point values	Diclofenac 1% gel			
Subject group type	Reporting group			
Number of subjects analysed	146[68]			
Units: Score				
median (full range (min-max))				
Day 2 (Visit 2)	-2.4 (-47.6 to 47.6)			
Day 4 (Visit 3)	-15.2 (-69.1 to 35.7)			
Day 7 (Visit 4)	-26.2 (-85.7 to 22.6)			
Day 14 (Visit 5)	-39.5 (-95.2 to 7.1)			

Notes:

[68] - Per Protocol analysis set n=615

Statistical analyses

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 2 (Visit 2)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set; FAS n=622.
FAAM-ADL Subscale (normalis. of mean, %max neg score), Change from Baseline, Last Observation Carried Forward (LOCF)

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0093
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D2V2

Statistical analysis description:

Time point: Day 2 (Visit 2) - D2V2
Hypothesis no. 1 (superiority) is based on the Full Analysis Set; FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[69]
P-value	= 0.0002
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.6062

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5538
upper limit	0.6587

Notes:

[69] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 4 (Visit 3)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set; FAS n=622.
FAAM-ADL Subscale (normalis. of mean, %max neg score), Change from Baseline, Last Observation Carried Forward (LOCF)

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D4V3

Statistical analysis description:

Time point: Day 4 (Visit 3) - D4V3
Hypothesis no. 1 (superiority) is based on the Full Analysis Set; FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[70]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.6516
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5993
upper limit	0.704

Notes:

[70] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 7 (Visit 4)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set; FAS n=622.
FAAM-ADL Subscale (normalis. of mean, %max neg score), Change from Baseline, Last Observation Carried Forward (LOCF)

Comparison groups	Traumed gel v Placebo gel

Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D7V4

Statistical analysis description:

Time point: Day 7 (Visit 4) - D7V4
Hypothesis no. 1 (superiority) is based on the Full Analysis Set; FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[71]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.6335
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5812
upper limit	0.6859

Notes:

[71] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 14 (Visit 5)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set; FAS n=622.
FAAM-ADL Subscale (normalis. of mean, %max neg score), Change from Baseline, Last Observation Carried Forward (LOCF)

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D14

Statistical analysis description:

Time point: Day 14 (Visit 5) - D14V5
Hypothesis no. 1 (superiority) is based on the Full Analysis Set; FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel

Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[72]
P-value	= 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.6092
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5561
upper limit	0.6623

Notes:

[72] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 2 (Visit 2)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
FAAM-ADL Subscale (normalis. of mean, %max neg score), Change from Baseline, Last Observation Carried Forward (LOCF)

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2868
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney), 2-Sided 95.0% CI D2V2

Statistical analysis description:

Time point: Day 2 (Visit 2) - D2V2
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[73]
P-value	= 0.0526
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5562
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5016
upper limit	0.6107

Notes:

[73] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 4 (Visit 3)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
FAAM-ADL Subscale (normalis. of mean, %max neg score), Change from Baseline, Last Observation Carried Forward (LOCF)

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.106
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney), 2-Sided 95.0% CI D4V3

Statistical analysis description:

Time point: Day 4 (Visit 3) - D4V3
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[74]
P-value	= 0.0306
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5629
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5077
upper limit	0.6181

Notes:

[74] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 7 (Visit 4)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
FAAM-ADL Subscale (normalis. of mean, %max neg score), Change from Baseline, Last Observation Carried Forward (LOCF)

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0864
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney), 2-Sided 95.0% CI D7V4

Statistical analysis description:

Time point: Day 7 (Visit 4) - D7V4
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[75]
P-value	= 0.0657
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5534
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.498
upper limit	0.6088

Notes:

[75] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 14 (Visit 5)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
FAAM-ADL Subscale (normalis. of mean, %max neg score), Change from Baseline, Last Observation Carried Forward (LOCF)

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1236
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney), 2-Sided 95.0% CI D14

Statistical analysis description:

Time point: Day 14 (Visit 5) - D14V5
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[76]
P-value	= 0.1754
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.5393
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4836
upper limit	0.5951

Notes:

[76] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Secondary: Amount of rescue medication (doses)

End point title	Amount of rescue medication (doses)

End point description:

Use of rescue medication was documented in the eCRF based on the information given in the patient diary and the drug accountability for rescue medication during the trial. Paracetamol (acetaminophen), 500 mg/tablet when necessary for pain with a maximum of 4 tablets or 2000 mg/day (but not more than 2 tablets at a time), was permitted as rescue medication for relieving pain in all three treatment groups. Patients were not allowed to take paracetamol within 8 h prior to Day 2 (Visit 2). For further Visits the restriction was 24 h. The number of tablets taken was validated summarised up to the Visit for analysis (absolute values are shown). Analysis was based on Full Analysis Set n=622 and Per Protocol analysis set n=615.

End point type	Secondary

End point timeframe:

Number paracetamol taken until visit Day 4 (Visit 3), Day 7 (Visit 4, End of Treatment) and Day 14 (Visit 5, Final Visit)

End point values	Traumed gel	Diclofenac 1% gel	Placebo gel	Traumed gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	316[77]	151[78]	155[79]	314[80]
Units: Tablets				
arithmetic mean (standard deviation)				
Day 4 (Visit 3)	0.5 (± 1.68)	0.3 (± 1.20)	0.3 (± 1.32)	0.3 (± 0.97)
Day 7 (Visit 4)	0.7 (± 2.27)	0.4 (± 1.62)	0.4 (± 1.90)	0.4 (± 1.34)
Day 14 (Visit 5)	0.8 (± 3.11)	0.5 (± 1.92)	0.5 (± 2.23)	0.6 (± 1.92)

Notes:

[77] - Full Analysis Set n=622

[78] - Full Analysis Set n=622

[79] - Full Analysis Set n=622

[80] - Per Protocol analysis set n=615

End point values	Diclofenac 1% gel			
Subject group type	Reporting group			
Number of subjects analysed	146[81]			
Units: Tablets				
arithmetic mean (standard deviation)				
Day 4 (Visit 3)	0.2 (± 0.61)			
Day 7 (Visit 4)	0.2 (± 0.77)			
Day 14 (Visit 5)	0.2 (± 0.98)			

Notes:

[81] - Per Protocol analysis set n=615

Statistical analyses

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 4 (Visit 3)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set; FAS n=622.

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0998
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D4V3

Statistical analysis description:

Time point: Day 4 (Visit 3) - D4V3
Hypothesis no. 1 (superiority) is based on the Full Analysis Set; FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[82]
P-value	= 0.0916
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.4731
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4442
upper limit	0.5021

Notes:

[82] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 7 (Visit 4)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set; FAS n=622.

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1794
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D7V4

Statistical analysis description:

Time point: Day 7 (Visit 4) - D7V4
Hypothesis no. 1 (superiority) is based on the Full Analysis Set; FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel

Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[83]
P-value	= 0.3204
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.4836
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4523
upper limit	0.5148

Notes:

[83] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 14 (Visit 5)

Statistical analysis description:

Hypothesis no. 1 (superiority) is based on the Full Analysis Set; FAS n=622.

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1643
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D14

Statistical analysis description:

Time point: Day 14 (Visit 5) - D14V5
Hypothesis no. 1 (superiority) is based on the Full Analysis Set; FAS n=622.
CI, Confidence interval

Comparison groups	Traumed gel v Placebo gel
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[84]
P-value	= 0.3745
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.4854
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4543
upper limit	0.5165

Notes:

[84] - Superiority is defined for LB-MW>0.50.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 4 (Visit 3)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0451
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D4V3

Statistical analysis description:

Time point: Day 4 (Visit 3) - D4V3
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[85]
P-value	= 0.0383
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.467
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4391
upper limit	0.4949

Notes:

[85] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 7 (Visit 4)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0346
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D7V4

Statistical analysis description:

Time point: Day 7 (Visit 4) - D7V4
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel

Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[86]
P-value	= 0.0253
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.4638
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4357
upper limit	0.4919

Notes:

[86] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Statistical analysis title	Parametric Analysis (ANCOVA) - Day 14 (Visit 5)

Statistical analysis description:

Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0462
Method	ANCOVA

Statistical analysis title	Effect Sizes (Mann-Whitney); 2-Sided 95.0% CI D14

Statistical analysis description:

Time point: Day 14 (Visit 5) - D14V5
Hypothesis no. 2 (non-inferiority) is based on the Per Protocol (PP) analysis set; PP n=615.
CI, Confidence interval

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[87]
P-value	= 0.052
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney estimator
Point estimate	0.4685
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4398
upper limit	0.4972

Notes:

[87] - Non-inferiority is defined for LB-MW>0.407.
LB, Lower Bound of the two-sided confidence interval; MW, Mann-Whitney estimator

Secondary: Time to 50% improvement of pain at rest measured by Visual Analog Scale (VAS)

End point title	Time to 50% improvement of pain at rest measured by Visual Analog Scale (VAS)

End point description:

In accordance with the final Statistical Analysis Plan, the time to 50% improvement of pain was evaluated for both, pain on passive movement and pain at rest at all patient visits using the percent change from Baseline (recorded at Day 1). The time to 50% improvement (stable) of pain at rest (days) was calculated from the VAS raw data, based on the actual date and time of pain measurements. In case of missing data for time to 50% improvement (no 50% improvement reached during observational period) the variable was technically evaluated as 'censored' observation with replacement of missing days by the last existing visit. The analysis was based on Full Analysis Set n=622 and Per Protocol analysis set n=615. Absolute values are shown.

End point type	Secondary

End point timeframe:

Baseline (Visit 1) to Day 14 (Visit 5, Final Visit)

End point values	Traumed gel	Diclofenac 1% gel	Placebo gel	Traumed gel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	316[88]	151[89]	155[90]	314[91]
Units: Days				
median (full range (min-max))				
Time to 50% Improvement (Stable) of Pain at Rest	3.99 (0.89 to 14.89)	5.46 (0.94 to 14.20)	6.00 (0.96 to 14.84)	3.99 (0.89 to 14.89)

Notes:

[88] - Full Analysis Set n=622

[89] - Full Analysis Set n=622

[90] - Full Analysis Set n=622

[91] - Per Protocol analysis set n=615

End point values	Diclofenac 1% gel			
Subject group type	Reporting group			
Number of subjects analysed	146[92]			
Units: Days				
median (full range (min-max))				
Time to 50% Improvement (Stable) of Pain at Rest	5.97 (0.94 to 14.20)			

Notes:

[92] - Per Protocol analysis set n=615

Statistical analyses

Statistical analysis title	Kaplan-Meier Function, Cumulative % with Event

Statistical analysis description:

Kaplan-Meier (KM) curves for time-to-event (including censored values) were performed and tested for group differences by means of the Peto-Logrank test (time-to-event (logrank) test) as specified in the protocol. Analysis based on Full Analysis Set (FAS); FAS n=622.

Comparison groups	Traumed gel v Placebo gel

Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[93]
P-value	= 0.0023
Method	Peto-Logrank

Notes:

[93] - KM curve shows a superiority of Traumed gel versus Placebo gel, with a difference of the two medians (KM function) by two days in favour of Traumed gel.

Statistical analysis title	Kaplan-Meier Function, Cumulative % with Event

Statistical analysis description:

Kaplan-Meier (KM) curves for time-to-event (including censored values) were performed and tested for group differences by means of the Peto-Logrank test (time-to-event (logrank) test) as specified in the protocol. Analysis based on Per Protocol (PP) analysis set; PP n=615.

Comparison groups	Traumed gel v Diclofenac 1% gel
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[94]
P-value	= 0.2481
Method	Peto-Logrank

Notes:

[94] - KM curve shows a slight superiority of Traumed gel versus Diclofenac gel, with a difference of the two medians (KM function) by two days in favour of Traumed gel.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were assessed at each Visit: Baseline Visit 1, Visit 2 (Day 2), Visit 3 (Day 4), Visit 4 (Day 7, End of Treatment) to Visit 5 (Day 14, Final Visit).

Adverse event reporting additional description:

AE collection/reporting in eCRF during entire trial. They were patient-reported, elicited by investigator (INV) questioning, detected through physical examination/other means. AE description by duration, start/end, intensity, INV causality, action/s taken, concomitant diseases/resp. medication in general start, end/dosage rescue medication outcome.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Traumed gel

Reporting group description:

Patients receiving test product. No safety exclusions from randomised population: total safety data set equals randomised population (n=625; main Clinical Trial Report population).

Reporting group title	Diclofenac 1% gel

Reporting group description:

Patients receiving reference product. No safety exclusions from randomised population: total safety data set equals randomised population (n=625; main Clinical Trial Report population).

Reporting group title	Placebo gel

Reporting group description:

Patients receiving Placebo. No safety exclusions from randomised population: total safety data set equals randomised population (n=625; main Clinical Trial Report population).

Serious adverse events	Traumed gel	Diclofenac 1% gel	Placebo gel
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 318 (0.00%)	1 / 152 (0.66%)	0 / 155 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Upper Arm Fracture (Humerus Fracture) right			
subjects affected / exposed	0 / 318 (0.00%)	1 / 152 (0.66%)	0 / 155 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Traumed gel	Diclofenac 1% gel	Placebo gel
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 318 (2.83%)	2 / 152 (1.32%)	6 / 155 (3.87%)
Injury, poisoning and procedural complications			
Weber a Frakture			
subjects affected / exposed	1 / 318 (0.31%)	0 / 152 (0.00%)	0 / 155 (0.00%)
occurrences (all)	1	0	0
Distorsion Forefoot			
subjects affected / exposed	1 / 318 (0.31%)	0 / 152 (0.00%)	0 / 155 (0.00%)
occurrences (all)	1	0	0
Sacroiliac sprain			
subjects affected / exposed	0 / 318 (0.00%)	0 / 152 (0.00%)	1 / 155 (0.65%)
occurrences (all)	0	0	1
Nervous system disorders			
Migraine			
subjects affected / exposed	1 / 318 (0.31%)	0 / 152 (0.00%)	0 / 155 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 318 (0.31%)	0 / 152 (0.00%)	0 / 155 (0.00%)
occurrences (all)	3	0	0
Tension Headache			
subjects affected / exposed	1 / 318 (0.31%)	0 / 152 (0.00%)	0 / 155 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Application site burning after prerious existing mosquito bite			
subjects affected / exposed	0 / 318 (0.00%)	0 / 152 (0.00%)	1 / 155 (0.65%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 318 (0.00%)	0 / 152 (0.00%)	1 / 155 (0.65%)
occurrences (all)	0	0	1
Dry skin over treated (skin) area			
subjects affected / exposed	1 / 318 (0.31%)	2 / 152 (1.32%)	0 / 155 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			

Neck pain			
subjects affected / exposed	1 / 318 (0.31%)	0 / 152 (0.00%)	0 / 155 (0.00%)
occurrences (all)	1	0	0
Knee pain left			
subjects affected / exposed	0 / 318 (0.00%)	0 / 152 (0.00%)	1 / 155 (0.65%)
occurrences (all)	0	0	1
Infections and infestations			
Akute nasopharyngitis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 152 (0.00%)	1 / 155 (0.65%)
occurrences (all)	0	0	1
Common cold			
subjects affected / exposed	1 / 318 (0.31%)	0 / 152 (0.00%)	1 / 155 (0.65%)
occurrences (all)	1	0	1
Abscess ellebow right			
subjects affected / exposed	1 / 318 (0.31%)	0 / 152 (0.00%)	0 / 155 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 February 2020	Amendment to protocol version 3.0: Sample size was enhanced following German Competent Authority (BfArM) recommendation to compensate cases for whom maintenance of blinding procedures could have been not adhered to as planned. Final sample size was enhanced to n=202 patients for Diclofenac 1% gel and Placebo gel each and to n=404 patients for the Traumed gel group. New total planned patient number was n=808. Reason: To ensure planned power and internal validity for evaluating the predefined trial objectives and reaching unbiased conclusions by including only those cases in the analysis sample with blinding compliance fully confirmed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 December 2019	The trial was not prematurely terminated but enrolment was suspended due to lack of investigational medicinal product from Dec 2019 to Feb 2020.	17 February 2020
23 March 2020	The trial was not prematurely terminated but enrolment was suspended due to the SARS-CoV-2 pandemic from Mar 2020 to Jun 2020.	25 June 2020

Notes:

Limitations and caveats

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

NA

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23889885