Clinical trial results:
Comparison of the Efficacy of Diclofenac Sodium Topical Gel, 1% (Mylan) to Voltaren® Gel, 1% (Novartis US) and Placebo in Adult Subjects with Knee Osteoarthritis

Summary

EudraCT number	2012-002682-36
Trial protocol	HU
Global end of trial date	30 August 2013

Results information

Result version number	v1 (current)
This version publication date	06 March 2020
First version publication date	06 March 2020

Trial information

Trial identification

Sponsor protocol code	DGEL-12058

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Mylan Pharmaceuticals Inc
Sponsor organisation address	3711, Collins Ferry Road, Morgantown, United States,
Public contact	Clinical Trial Information Desk, Mylan Pharmaceuticals Inc, 001 304554-6693,
Scientific contact	Clinical Trial Information Desk, Mylan Pharmaceuticals Inc, 001 304554-6693,

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	06 February 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to investigate the clinical endpoint bioequivalence of Mylan's Diclofenac Sodium Topical Gel, 1% compared to Novartis US' Voltaren® Gel, 1% and placebo (vehicle, Mylan) following multiple topical applications of 4 g to a single osteoarthritic knee (4 g four times daily for 4 weeks).

Protection of trial subjects:

Study had a placebo control arm. Study allowed rescue medication use. Rescue medication was also allowed for the treatment of aches and pains unrelated to knee pain.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2012
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	Ukraine: 66
Country: Number of subjects enrolled	Romania: 145
Country: Number of subjects enrolled	Poland: 763
Country: Number of subjects enrolled	Hungary: 288
Worldwide total number of subjects	1262
EEA total number of subjects	1196

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)	756

From 65 to 84 years	504
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After eligibility assessment at screening, patients were requested to discontinue their current OA therapy for a period of at least 7 days (or >5 half lives of the current therapy). Rescue medication was provided during this period and were requested to temporarily withdraw rescue medication use 24 hours prior to assessment visits

Period 1

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

Blinding implementation details:

The packaging of test, reference, and placebo investigational products was similar in appearance to make difference in treatment less obvious to the subjects and to maintain adequate blinding of evaluators.

Arms

Are arms mutually exclusive?	Yes
Arm title	Test

Arm description:

Test diclofenac sodium topical gel 1% (Mylan)

Arm type	Experimental
Investigational medicinal product name	Diclofenac sodium topical gel 1%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

4 g four times daily for 4 weeks).

Arm title	Reference

Arm description:

Voltaren Gel 1%

Arm type	Active comparator
Investigational medicinal product name	Voltaren® Gel 1%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

4 g four times daily for 4 weeks

Arm title	Placebo

Arm description:

Placebo gel

Arm type	Placebo

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

Dosage and administration details:

4 g four times daily for 4 weeks

Number of subjects in period 1[1]	Test	Reference	Placebo
Started	421	417	418
Completed	390	392	393
Not completed	31	25	25
Adverse event, serious fatal	-	2	-
Consent withdrawn by subject	7	6	5
Other event	2	-	-
Adverse event, non-fatal	7	4	5
Lost to follow-up	3	1	1
Lack of efficacy	2	2	2
Protocol deviation	10	10	12

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: There were 6 patients (0 in Test Arm, 2 in Reference arm and 4 in Placeo arm) who were randomized but did not receive treatment. The reasons are not readily available in the CSR. These patients were not part of the safety population set. All tables and data analysis in the CSR are based on safety population and hence there is a discrepancy in total enrolled and the baseline numbers.

Baseline characteristics

Reporting groups	
Reporting group title	Test
Reporting group description:	
Test diclofenac sodium topical gel 1% (Mylan)	
Reporting group title	Reference
Reporting group description:	
Voltaren Gel 1%	
Reporting group title	Placebo
Reporting group description:	
Placebo gel	

Reporting group values	Test	Reference	Placebo
Number of subjects	421	417	418
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	260	251	241
From 65-84 years	161	165	176
85 years and over	0	1	1
Gender categorical Units: Subjects			
Female	327	318	315
Male	94	99	103
Baseline VAS			
Baseline VAS			
Units: mm			
arithmetic mean	74.7	74.6	74.2
standard deviation	± 11.7	± 12.1	± 11.6

Reporting group values	Total		
Number of subjects	1256		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		

Adults (18-64 years)	752		
From 65-84 years	502		
85 years and over	2		
Gender categorical Units: Subjects			
Female	960		
Male	296		
Baseline VAS			
Baseline VAS			
Units: mm arithmetic mean standard deviation	- -		

End points

End points reporting groups	
Reporting group title	Test
Reporting group description: Test diclofenac sodium topical gel 1% (Mylan)	
Reporting group title	Reference
Reporting group description: Voltaren Gel 1%	
Reporting group title	Placebo
Reporting group description: Placebo gel	

Primary: Mean change from baseline to Week 4 in WOMAC pain score	
End point title	Mean change from baseline to Week 4 in WOMAC pain score
End point description:	
End point type	Primary
End point timeframe: Week 4	

End point values	Test	Reference	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	400[1]	395[2]	398[3]	
Units: Units				
least squares mean (standard error)	-6.41 (± 0.20)	-6.64 (± 0.20)	-6.38 (± 0.20)	

Notes:
[1] - mITT
[2] - mITT
[3] - mITT

Statistical analyses

Statistical analysis title	Therapeutic Equivalence between Test and Reference
Comparison groups	Test v Reference
Number of subjects included in analysis	795
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	LS Means Ratio
Point estimate	0.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.908
upper limit	1.032

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Week 4	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1
Reporting groups	
Reporting group title	Test
Reporting group description: Test diclofenac sodium topical gel 1% (Mylan)	
Reporting group title	Reference
Reporting group description: Voltaren Gel 1%	
Reporting group title	Placebo
Reporting group description: Placebo gel	

Serious adverse events	Test	Reference	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 421 (0.00%)	0 / 417 (0.00%)	2 / 418 (0.48%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events	0	0	2
Nervous system disorders			
Meningitis bacterial			
subjects affected / exposed	0 / 421 (0.00%)	0 / 417 (0.00%)	1 / 418 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 421 (0.00%)	0 / 417 (0.00%)	1 / 418 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Test	Reference	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	158 / 421 (37.53%)	154 / 417 (36.93%)	152 / 418 (36.36%)
Nervous system disorders			
Headache			
subjects affected / exposed	93 / 421 (22.09%)	89 / 417 (21.34%)	94 / 418 (22.49%)
occurrences (all)	251	243	220
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	35 / 421 (8.31%)	40 / 417 (9.59%)	28 / 418 (6.70%)
occurrences (all)	63	82	66
Back pain			
subjects affected / exposed	21 / 421 (4.99%)	14 / 417 (3.36%)	16 / 418 (3.83%)
occurrences (all)	47	29	33
Spinal pain			
subjects affected / exposed	16 / 421 (3.80%)	16 / 417 (3.84%)	20 / 418 (4.78%)
occurrences (all)	28	28	42
Pain in extremity			
subjects affected / exposed	10 / 421 (2.38%)	18 / 417 (4.32%)	14 / 418 (3.35%)
occurrences (all)	24	30	28
Musculoskeletal pain			
subjects affected / exposed	8 / 421 (1.90%)	6 / 417 (1.44%)	9 / 418 (2.15%)
occurrences (all)	19	10	12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported