Clinical trial results:
A multicentre, comparative, randomised, double-blind, double-dummy clinical trial on the efficacy and safety of Condrosulf® versus Celebrex® and versus a placebo in the treatment of knee osteoarthritis

Summary

EudraCT number	2013-001619-62
Trial protocol	IT BE CZ PL
Global end of trial date	19 October 2015

Results information

Result version number	v1 (current)
This version publication date	06 May 2022
First version publication date	06 May 2022
Summary attachment (see zip file)	annrheumdis-2016-210860.full (annrheumdis-2016-210860.full.pdf)

Trial information

Trial identification

Sponsor protocol code	12EU/Ct06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02079727
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IBSA, Institut Biochimique S.A.
Sponsor organisation address	Via del Piano, Pambio-Noranco, Switzerland, 6915
Public contact	Giuseppe Mautone, IBSA, Institut Biochimique S.A., 0041 0583601000, sd@ibsa.ch
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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 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 October 2015
Global end of trial reached?	Yes
Global end of trial date	19 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

assess the superiority of Condrosulf 800 mg once daily versus placebo for 182 days. Celebrex will be used as active control. The primary endpoints will be a change in the Lequesne algo-functional index and a change in the VAS from day 1 to day 182

Protection of trial subjects:

Patients have rescue medication available in case of uncontrolled pain.
Patients can stop the study at any time.

Background therapy: -

Evidence for comparator:

Celebrex® 200 mg (celecoxib) was used as active comparator.

Actual start date of recruitment	12 June 2014
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	Poland: 493
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Czechia: 74
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Switzerland: 17
Worldwide total number of subjects	603
EEA total number of subjects	586

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)	276
From 65 to 84 years	325
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 16 centres in 5 European countries (1 in Belgium, 3 in Switzerland, 1 in Italy, 5 in Poland and 6 in Czech Republic).
First patient enrolled: 12 June 2014; Last patient completed: 19 October 2015

Pre-assignment

Screening details:

656 patients have been screened of which 52 Screening failure.
604 patients have been randomized. Of these, 505 patients completed the study and 99 interrupted it prematurely

Period 1

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

Blinding implementation details:

The realization of the double-blind, double dummy design was made possible by the production of matched placebo tablets and capsules that were identical to the active product Condrosulf and to the overencapsulated Celebrex, respectively, in terms of size, shape, colour and method of administration.

Arms

Are arms mutually exclusive?	Yes
Arm title	Condrosulf

Arm description:

Group 1: one tablet of Condrosulf® 800 mg and 1 capsule of Placebo of Celebrex®, once a day by oral route.

Arm type	Experimental
Investigational medicinal product name	Condrosulf® 800 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet of Condrosulf® 800 mg once a day by oral route.
Being a double dummy study the patient also took 1 capsule of Placebo of Celebrex®, once a day by oral route
Tablets and capsules had to be swallowed whole with a glass of water without chewing them.

Arm title	Celebrex® 200 mg

Arm description:

Group 2: One tablet of Placebo of Condrosulf® and 1 capsule of Celebrex® 200 mg, once a day by oral route

Arm type	Active comparator
Investigational medicinal product name	Celebrex®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 capsule of Celebrex® 200 mg, once a day by oral route;
Being it a double dummy study, the patient also took one tablet of Placebo of Condrosulf® , once a day by oral route;
Tablets and capsules had to be swallowed whole with a glass of water without chewing them.

Arm title	Placebo

Arm description:

Group 3: one tablet of Placebo of Condrosulf® and 1 capsule of Placebo of Celebrex®, once a day by oral route.

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

Dosage and administration details:

Patient take one tablet of Placebo of Condrosulf® and 1 capsule of Placebo of Celebrex®, once a day by oral route.
Tablets and capsules had to be swallowed whole with a glass of water without chewing them.

Number of subjects in period 1	Condrosulf	Celebrex® 200 mg	Placebo
Started	199	199	205
Completed	160	173	172
Not completed	39	26	33
Consent withdrawn by subject	15	5	14
Adverse event, non-fatal	9	12	6
Lack of efficacy	12	9	12
Protocol deviation	3	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Condrosulf
Reporting group description:	
Group 1: one tablet of Condrosulf® 800 mg and 1 capsule of Placebo of Celebrex®, once a day by oral route.	

Reporting group title	Celebrex® 200 mg
Reporting group description:	
Group 2: One tablet of Placebo of Condrosulf® and 1 capsule of Celebrex® 200 mg, once a day by oral route	

Reporting group title	Placebo
Reporting group description:	
Group 3: one tablet of Placebo of Condrosulf® and 1 capsule of Placebo of Celebrex®, once a day by oral route.	

Reporting group values	Condrosulf	Celebrex® 200 mg	Placebo
Number of subjects	199	199	205
Age categorical Units: Subjects			
Adults (18-64 years)	88	89	99
From 65-84 years	110	109	106
85 years and over	1	1	0
Age continuous Units: years			
arithmetic mean	65.5	65.5	64.9
standard deviation	± 8	± 7.78	± 8.04
Gender categorical Units: Subjects			
Female	156	160	152
Male	43	39	53
Lequesne'index			
Lequesne’s algo-functional index			
Units: score			
arithmetic mean	11.78	11.59	11.79
standard deviation	± 2.948	± 2.886	± 3.047

Reporting group values	Total		
Number of subjects	603		
Age categorical Units: Subjects			
Adults (18-64 years)	276		
From 65-84 years	325		
85 years and over	2		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical Units: Subjects			
Female	468		
Male	135		
Lequesne'index			
Lequesne’s algo-functional index			
Units: score arithmetic mean standard deviation	- 		

Subject analysis sets

Subject analysis set title	Intent-to-treat (ITT) population 1
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intent-to-treat (ITT) population 1, which consisted of all randomised patients who received the study medication and had at least one post-baseline efficacy evaluation (1 month of treatment)	
Subject analysis set title	ITT population 2
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITT population 2, which consisted of all randomised patients who received the study medication	
Subject analysis set title	Per-Protocol (PP) population
Subject analysis set type	Per protocol
Subject analysis set description: Per-Protocol (PP) population, which consisted of all patients in the ITT population who did not have any major protocol violations	

Reporting group values	Intent-to-treat (ITT) population 1	ITT population 2	Per-Protocol (PP) population
Number of subjects	591	603	534
Age categorical Units: Subjects			
Adults (18-64 years)		276	
From 65-84 years		325	
85 years and over		2	
Age continuous Units: years			
arithmetic mean	65.3	65.3	65.2
standard deviation	± 7.86	± 7.93	± 7.83
Gender categorical Units: Subjects			
Female	130	135	120
Male	461	468	414
Lequesne'index			
Lequesne’s algo-functional index			
Units: score arithmetic mean standard deviation	 ±	 ±	 ±

End points

End points reporting groups

Reporting group title	Condrosulf
Reporting group description:	
Group 1: one tablet of Condrosulf® 800 mg and 1 capsule of Placebo of Celebrex®, once a day by oral route.	

Reporting group title	Celebrex® 200 mg
Reporting group description:	
Group 2: One tablet of Placebo of Condrosulf® and 1 capsule of Celebrex® 200 mg, once a day by oral route	
Reporting group title	Placebo
Reporting group description:	
Group 3: one tablet of Placebo of Condrosulf® and 1 capsule of Placebo of Celebrex®, once a day by oral route.	
Subject analysis set title	Intent-to-treat (ITT) population 1
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intent-to-treat (ITT) population 1, which consisted of all randomised patients who received the study medication and had at least one post-baseline efficacy evaluation (1 month of treatment)	
Subject analysis set title	ITT population 2
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT population 2, which consisted of all randomised patients who received the study medication	
Subject analysis set title	Per-Protocol (PP) population
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-Protocol (PP) population, which consisted of all patients in the ITT population who did not have any major protocol violations	

Primary: Change in Lequesne’s algo-funct. index

End point title	Change in Lequesne’s algo-funct. index
End point description:	
The change in the Lequesne’s algo-functional index from Day 1 to Day 182	

End point type	Primary
End point timeframe:	
From Day 1 to 182	

End point values	Condrosulf	Celebrex® 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	185	191	191	
Units: Score				
arithmetic mean (standard deviation)	-4.51 (± 3.677)	-4.30 (± 3.587)	-3.59 (± 3.651)	

Statistical analyses

Statistical analysis title	LEQUESNE INDEX SCORE REDUCTION AT VISIT 4 ConVsPl

Statistical analysis description:

Analysis is based on an analysis of covariance model with mean change from baseline in the VAS score at last visit as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Comparison groups	Condrosulf v Placebo
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.914
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.567
upper limit	-0.261

Statistical analysis title	LEQUESNE INDEX SCORE REDUCTION AT VISIT 4 ConVsCel

Statistical analysis description:

Analysis is based on an analysis of covariance model with mean change from baseline in the VAS score at last visit as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Comparison groups	Condrosulf v Celebrex® 200 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.097
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.563
upper limit	0.757

Statistical analysis title	LEQUESNE INDEX SCORE REDUCTION AT VISIT 4 CelVsPL

Statistical analysis description:

Analysis is based on an analysis of covariance model with mean change from baseline in the VAS score at last visit as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Comparison groups	Placebo v Celebrex® 200 mg

Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.662
upper limit	-0.361

Primary: Change in the VAS pain (in mm.) from Day 1 to Day 182.	
End point title	Change in the VAS pain (in mm.) from Day 1 to Day 182.
End point description:	
Changeof pian on the VAS scale (in mm) from Day 1 to Day 182. Pain was measured on a horizontal visual analogical scale (VAS) of 100 mm going from 0 =absent pain, to 100 = maximum pain.	
End point type	Primary
End point timeframe:	
From Day 1 to Day 182	

End point values	Condrosulf	Celebrex® 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	185	191	191	
Units: mm				
arithmetic mean (standard deviation)	-39.8 (± 24.65)	-38.1 (± 24.26)	-32.4 (± 24.81)	

Statistical analyses

Statistical analysis title	PAIN (VAS) REDUCTION AT VISIT 4 CelVsPL
Statistical analysis description:	
Analysis is based on an analysis of covariance model with mean change from baseline in the VAS score at last visit as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.	
Comparison groups	Celebrex® 200 mg v Placebo
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-7.017

Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.696
upper limit	-2.338

Statistical analysis title	PAIN (VAS) REDUCTION AT VISIT 4 CondVsPL

Statistical analysis description:

Analysis is based on an analysis of covariance model with mean change from baseline in the VAS score at last visit as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Comparison groups	Placebo v Condrosulf
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-7.379
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.082
upper limit	-2.676

Statistical analysis title	PAIN (VAS) REDUCTION AT VISIT 4 CondVsCel

Statistical analysis description:

Analysis is based on an analysis of covariance model with mean change from baseline in the VAS score at last visit as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Comparison groups	Celebrex® 200 mg v Condrosulf
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.362
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.113
upper limit	4.39

Secondary: Clinically important improvement (MCII)	
End point title	Clinically important improvement (MCII)
End point description: Assessment of minimal clinically important improvement (MCII)	
End point type	Secondary
End point timeframe: From Day 1 to day 182	

End point values	Condrosulf	Celebrex® 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	192	195	204	
Units: Subjects				
Responder	136	137	125	
No Responder	56	58	79	

Statistical analyses

Statistical analysis title	PATIENT REACHING THE MCII AT VISIT 4 ConVsPl
Statistical analysis description: SECONDARY EFFICACY ANALYSIS: PROPORTIONS OF PATIENTS REACHING THE MINIMAL CLINICALLY IMPORTANT IMPROVEMENT(MCII) INTENT-TO-TREAT POPULATION 1	
Comparison groups	Placebo v Condrosulf
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.156
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.003
upper limit	1.332
Variability estimate	Standard error of the mean
Dispersion value	0.072

Statistical analysis title	PATIENT REACHING THE MCII AT VISIT 4 CelVsPl
Statistical analysis description: SECONDARY EFFICACY ANALYSIS: PROPORTIONS OF PATIENTS REACHING THE MINIMAL CLINICALLY IMPORTANT IMPROVEMENT(MCII) INTENT-TO-TREAT POPULATION 1	
Comparison groups	Placebo v Celebrex® 200 mg

Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.147
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.995
upper limit	1.322
Variability estimate	Standard error of the mean
Dispersion value	0.073

Statistical analysis title	PATIENT REACHING THE MCII AT VISIT 4 ConVsCel
Statistical analysis description:	
SECONDARY EFFICACY ANALYSIS: PROPORTIONS OF PATIENTS REACHING THE MINIMAL CLINICALLY IMPORTANT IMPROVEMENT(MCII) INTENT-TO-TREAT POPULATION 1	
Comparison groups	Condrosulf v Celebrex® 200 mg
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.886
upper limit	1.147
Variability estimate	Standard error of the mean
Dispersion value	0.066

Secondary: Consumption of paracetamol	
End point title	Consumption of paracetamol
End point description:	
Consumption of paracetamol (noted in a diary);	
End point type	Secondary
End point timeframe:	
From Day 1 to day 182	

End point values	Condrosulf	Celebrex® 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	192	195	204	
Units: Total dose (n. of tablets)				
arithmetic mean (standard deviation)	86.4 (± 147.37)	73.2 (± 114.87)	90.6 (± 129.67)	

Statistical analyses

Statistical analysis title	TOTAL CONSUMPTION OF RESCUE MED AT VISIT4 CondVsPL
Statistical analysis description: TOTAL CONSUMPTION OF RESCUE MEDICATION (TOTAL DOSE - N. of TABLETS)	
Comparison groups	Placebo v Condrosulf
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.185
upper limit	23.185

Statistical analysis title	TOTAL CONSUMPTION OF RESCUE MED AT VISIT4 CelVsPL
Statistical analysis description: TOTAL CONSUMPTION OF RESCUE MEDICATION (TOTAL DOSE - N. of TABLETS)	
Comparison groups	Placebo v Celebrex® 200 mg
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-17.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.551
upper limit	6.751

Statistical analysis title	TOTAL CONSUMPTION OF RESCUEMED AT VISIT4 CondVsCeL

Statistical analysis description:	
TOTAL CONSUMPTION OF RESCUE MEDICATION (TOTAL DOSE - N. of TABLETS)	
Comparison groups	Condrosulf v Celebrex® 200 mg
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	13.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.186
upper limit	39.586

Secondary: Global efficacy assessment	
End point title	Global efficacy assessment
End point description:	
Global efficacy assessment by the patient and the Investigator	
End point type	Secondary
End point timeframe:	
Day 30, 91 and 182	

End point values	Condrosulf	Celebrex® 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	192	195	204	
Units: Subjects				
None	21	22	37	
Poor	26	26	30	
Fair	45	47	53	
Good	79	76	69	
Excellent	21	24	15	

Statistical analyses

Statistical analysis title	OVERALL TREATMENT EFFICACY AT VISIT 4 CondVsPL
Statistical analysis description:	
OVERALL TREATMENT EFFICACY JUDGED BY THE PATIENT	
Comparison groups	Condrosulf v Placebo

Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mantel-Haenszel

Statistical analysis title	OVERALL TREATMENT EFFICACY AT VISIT 4 CelVsPL
Statistical analysis description: OVERALL TREATMENT EFFICACY JUDGED BY THE PATIENT	
Comparison groups	Placebo v Celebrex® 200 mg
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mantel-Haenszel

Statistical analysis title	OVERALL TREATMENT EFFICACY AT VISIT 4 CondVsCel
Statistical analysis description: OVERALL TREATMENT EFFICACY JUDGED BY THE PATIENT	
Comparison groups	Condrosulf v Celebrex® 200 mg
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mantel-Haenszel

Secondary: PATIENTS REACHING THE PATIENT ACCEPTABLE SYMPTOM STATE (PASS)

End point title	PATIENTS REACHING THE PATIENT ACCEPTABLE SYMPTOM STATE (PASS)
End point description: PROPORTIONS OF PATIENTS REACHING THE PATIENT ACCEPTABLE SYMPTOM STATE (PASS)	
End point type	Secondary
End point timeframe: From baseline to Visit 4 (day 182)	

End point values	Condrosulf	Celebrex® 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	192	195	204	
Units: Subjects				
Responder	113	118	101	
No Responder	79	77	103	

Statistical analyses

Statistical analysis title	PATIENTS REACHING PASS AT VISIT 4 CondVsPL
Statistical analysis description: PROPORTIONS OF PATIENTS REACHING THE PATIENT ACCEPTABLE SYMPTOM STATE (PASS)	
Comparison groups	Condrosulf v Placebo
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.217
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.017
upper limit	1.458
Variability estimate	Standard error of the mean
Dispersion value	0.092

Statistical analysis title	PATIENTS REACHING PASS AT VISIT 4 CelVsPL
Statistical analysis description: PROPORTIONS OF PATIENTS REACHING THE PATIENT ACCEPTABLE SYMPTOM STATE (PASS)	
Comparison groups	Placebo v Celebrex® 200 mg
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.205
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.006
upper limit	1.443
Variability estimate	Standard error of the mean
Dispersion value	0.092

Statistical analysis title	PATIENTS REACHING PASS AT VISIT 4 CondVsCel
Statistical analysis description: PROPORTIONS OF PATIENTS REACHING THE PATIENT ACCEPTABLE SYMPTOM STATE (PASS)	
Comparison groups	Condrosulf v Celebrex® 200 mg
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.861
upper limit	1.186
Variability estimate	Standard error of the mean
Dispersion value	0.082

Secondary: Change in the Lequesne’s algo-functional index from Day 1 to Day 30	
End point title	Change in the Lequesne’s algo-functional index from Day 1 to Day 30
End point description: The change in the Lequesne’s algo-functional index from Day 1 to Day 30	
End point type	Secondary
End point timeframe: From Day 1 to Day 30	

End point values	Condrosulf	Celebrex® 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	183	186	196	
Units: Score				
arithmetic mean (standard deviation)	-2.24 (± 2.311)	-2.63 (± 2.631)	-2.09 (± 2.508)	

Statistical analyses

Statistical analysis title	LEQUESNE INDEX SCORE REDUCTION AT VISIT 2 CelVsPL
Comparison groups	Celebrex® 200 mg v Placebo

Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.524
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.998
upper limit	-0.051

Notes:

[1] - Analysis is based on an analysis of covariance model with mean change from baseline in the LEQUENE INDEX SCORE at visit 2 as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Statistical analysis title	LEQUESNE INDEX SCORE REDUCTION AT VISIT 2 ConVsPl
Comparison groups	Placebo v Condrosulf
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.147
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.622
upper limit	0.329

Notes:

[2] - Analysis is based on an analysis of covariance model with mean change from baseline in the LEQUENE INDEX SCORE at visit 2 as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Statistical analysis title	LEQUESNE INDEX SCORE REDUCTION AT VISIT 2 ConVsCel
Comparison groups	Condrosulf v Celebrex® 200 mg
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.377
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.103
upper limit	0.858

Notes:

[3] - Analysis is based on an analysis of covariance model with mean change from baseline in the LEQUENE INDEX SCORE at visit 2 as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Secondary: Change in the Lequesne's algo-functional index from Day 1 to Day 91

End point title	Change in the Lequesne's algo-functional index from Day 1 to Day 91

End point description:

The change in the Lequesne's algo-functional index from Day 1 to Day 91

End point type	Secondary

End point timeframe:

From Day 1 to Day 91

End point values	Condrosulf	Celebrex® 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	165	175	179	
Units: Score				
arithmetic mean (standard deviation)	-3.89 (± 3.215)	-3.77 (± 2.840)	-3.09 (± 2.835)	

Statistical analyses

Statistical analysis title	LEQUESNE INDEX SCORE REDUCTION AT VISIT 3 ConVsPl
Comparison groups	Condrosulf v Placebo
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.706
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.261
upper limit	-0.105

Notes:

[4] - Analysis is based on an analysis of covariance model with mean change from baseline in the LEQUENE INDEX SCORE at visit 2 as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Statistical analysis title	LEQUESNE INDEX SCORE REDUCTION AT VISIT 3 CelVsPL
Comparison groups	Placebo v Celebrex® 200 mg

Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.719
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.272
upper limit	-0.166

Notes:

[5] - Analysis is based on an analysis of covariance model with mean change from baseline in the LEQUENE INDEX SCORE at visit 2 as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Statistical analysis title	LEQUESNE INDEX SCORE REDUCTION AT VISIT 3 ConVsCel
Comparison groups	Celebrex® 200 mg v Condrosulf
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.547
upper limit	0.575

Notes:

[6] - Analysis is based on an analysis of covariance model with mean change from baseline in the LEQUENE INDEX SCORE at visit 2 as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Secondary: Change in the VAS pain (in mm.) from Day 1 to Day 30.

End point title	Change in the VAS pain (in mm.) from Day 1 to Day 30.

End point description:

Change of pian on the VAS scale (in mm) from Day 1 to Day 30. Pain was measured on a horizontal visual analogical scale (VAS) of 100 mm going from 0 = absent pain, to 100 = maximum pain.

End point type	Secondary

End point timeframe:

From Day 1 to Day 30.

End point values	Condrosulf	Celebrex® 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	183	186	196	
Units: VAS (mm.)				
arithmetic mean (standard deviation)	-22.6 (± 18.11)	-24 (± 19.2)	-21.1 (± 20.61)	

Statistical analyses

Statistical analysis title	PAIN (VAS) REDUCTION AT VISIT 2 CondVsPL
Comparison groups	Condrosulf v Placebo
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.177
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.819
upper limit	2.465

Notes:

[7] - Analysis is based on an analysis of covariance model with mean change from baseline in the VAS score at visit 2 as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Statistical analysis title	PAIN (VAS) REDUCTION AT VISIT 2 CelVsPL
Comparison groups	Placebo v Celebrex® 200 mg
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.508
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.131
upper limit	1.116

Notes:

[8] - Analysis is based on an analysis of covariance model with mean change from baseline in the VAS score at visit 2 as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Statistical analysis title	PAIN (VAS) REDUCTION AT VISIT 2 CondVsCel
Comparison groups	Celebrex® 200 mg v Condrosulf

Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.331
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.349
upper limit	5.01

Notes:

[9] - Analysis is based on an analysis of covariance model with mean change from baseline in the VAS score at visit 2 as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Secondary: Change in the VAS pain (in mm.) from Day 1 to Day 91

End point title	Change in the VAS pain (in mm.) from Day 1 to Day 91

End point description:

Change of pain on the VAS scale (in mm) from Day 1 to Day 91. Pain was measured on a horizontal visual analogical scale (VAS) of 100 mm going from 0 =absent pain, to 100 = maximum pain.

End point type	Secondary

End point timeframe:

From Day 1 to Day 91

End point values	Condrosulf	Celebrex® 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	165	175	179	
Units: VAS (mm.)				
arithmetic mean (standard deviation)	-34.1 (± 21.26)	-32.7 (± 22.04)	-30.2 (± 20.46)	

Statistical analyses

Statistical analysis title	PAIN (VAS) REDUCTION AT VISIT 3 CondVsPL
Comparison groups	Placebo v Condrosulf
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.778

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.999
upper limit	1.443

Notes:

[10] - Analysis is based on an analysis of covariance model with mean change from baseline in the VAS score at visit 3 as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Statistical analysis title	PAIN (VAS) REDUCTION AT VISIT 3 CondVsCel
Comparison groups	Condrosulf v Celebrex® 200 mg
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.316
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.949
upper limit	4.581

Notes:

[11] - Analysis is based on an analysis of covariance model with mean change from baseline in the VAS score at visit 3 as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Statistical analysis title	PAIN (VAS) REDUCTION AT VISIT 3 CelVsPla
Comparison groups	Celebrex® 200 mg v Placebo
Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.094
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.294
upper limit	1.106

Notes:

[12] - Analysis is based on an analysis of covariance model with mean change from baseline in the VAS score at visit 3 as dependent variable, treatment and centre as fixed effect and baseline as covariate. BOCF = baseline observation carried forward; LOCF = last observation carried forward. Missing values at the each visit have been replaced using the BOCF method.

Other pre-specified: Treatment compliance

End point title	Treatment compliance

End point description:

Treatment compliance

End point type	Other pre-specified

End point timeframe:

Day 30, 91, 182

End point values	Condrosulf	Celebrex® 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	192	195	204	
Units: Compliance mean %				
arithmetic mean (standard deviation)	95.3 (± 12.24)	96.9 (± 8.54)	96.8 (± 8.55)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
All over the study, from the signature of the Informed consent until the end of the study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Condrosulf
Reporting group description:	
Group 1: one tablet of Condrosulf® 800 mg and 1 capsule of Placebo of Celebrex®, once a day by oral route.	
Reporting group title	Celebrex® 200 mg
Reporting group description:	
Group 2: One tablet of Placebo of Condrosulf® and 1 capsule of Celebrex® 200 mg, once a day by oral route	
Reporting group title	Placebo
Reporting group description:	
Group 3: one tablet of Placebo of Condrosulf® and 1 capsule of Placebo of Celebrex®, once a day by oral route.	

Serious adverse events	Condrosulf	Celebrex® 200 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 199 (1.01%)	1 / 199 (0.50%)	2 / 205 (0.98%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	0 / 199 (0.00%)	0 / 199 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament operation			
subjects affected / exposed	1 / 199 (0.50%)	0 / 199 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			

subjects affected / exposed	0 / 199 (0.00%)	0 / 199 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 199 (0.50%)	1 / 199 (0.50%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mobility decreased			
subjects affected / exposed	1 / 199 (0.50%)	0 / 199 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
spinal column stenosis			
subjects affected / exposed	1 / 199 (0.50%)	0 / 199 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Condrosulf	Celebrex® 200 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 199 (36.68%)	70 / 199 (35.18%)	80 / 205 (39.02%)
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 199 (12.56%)	27 / 199 (13.57%)	22 / 205 (10.73%)
occurrences (all)	50	49	40
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	14 / 199 (7.04%)	12 / 199 (6.03%)	13 / 205 (6.34%)
occurrences (all)	17	13	13
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 199 (4.52%)	6 / 199 (3.02%)	14 / 205 (6.83%)
occurrences (all)	11	20	26
Back pain			

subjects affected / exposed	7 / 199 (3.52%)	4 / 199 (2.01%)	12 / 205 (5.85%)
occurrences (all)	19	4	17
Spinal pain			
subjects affected / exposed	17 / 199 (8.54%)	8 / 199 (4.02%)	12 / 205 (5.85%)
occurrences (all)	28	13	21
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 199 (9.05%)	27 / 199 (13.57%)	30 / 205 (14.63%)
occurrences (all)	19	30	36

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2014	One substantial protocol amendment was issued on 26 March 2014. The original protocol already excluded patients with cardiovascular risks. Following the Belgian IEC request, the protocol amendment was submitted to better reflect the cardiovascular and non-cardiovascular contraindications listed in the package leaflet for Celebrex, and to better ensure that patients with any risk of adverse events potentially related with the treatment with celecoxib would have been excluded from trial participation, including those with a history of heart attack, ischemic heart disease or cerebrovascular disease (including transient ischemic attacks) or those having or having had peripheral arterial disease or past surgery of peripheral arteries.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28533290