Clinical trial results:
A phase 2/3 placebo-controlled, double-blind, randomized, trial of Diclofenac Gel AMZ001 3.06 % for the treatment of knee osteoarthritis symptoms

Summary

EudraCT number	2018-001934-16
Trial protocol	DK CZ
Global end of trial date	09 July 2019

Results information

Result version number	v1 (current)
This version publication date	27 July 2020
First version publication date	27 July 2020

Trial information

Trial identification

Sponsor protocol code	AMZ001-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03691844
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amzell B.V.
Sponsor organisation address	Siriusdreef 41, Hoofddorp, Netherlands, 2132 WT
Public contact	Clinical Development, Amzell B.V., amzell-disclosure@amzell.com
Scientific contact	Clinical Development, Amzell B.V., amzell-disclosure@amzell.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	20 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 June 2019
Global end of trial reached?	Yes
Global end of trial date	09 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the change in pain intensity, in terms of the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) pain score of the target knee at week 4.

Protection of trial subjects:

The Subjects experiencing adverse events were followed-up by the investigator until resolution or until the medical condition of the subject was stable.

Background therapy:

The trial allowed paracetamol/acetaminophen tablets 500 mg up to 4 g per day to be used as analgesic rescue medication in case of intolerable pain during the trial.

Evidence for comparator:

The trial used a Placebo gel as a comparator in a double-blind setting and an exploratory comparator arm with Voltaren gel 1% as a single-blind component.

Actual start date of recruitment	04 October 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	Czech Republic: 231
Country: Number of subjects enrolled	Denmark: 103
Country: Number of subjects enrolled	United States: 110
Worldwide total number of subjects	444
EEA total number of subjects	334

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)	216
From 65 to 84 years	227
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from seven trial sites in Denmark (1 site), Czech Republic (3 sites) and the USA (3 sites).

Pre-assignment

Screening details:

A total of 801 subjects were screened for the trial. 319 subjects failed to meet the eligibility criteria, 38 subjects discontinued before randomisation.

Period 1

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

Blinding implementation details:

All double-blind Investigational products were indistinguishable in appearance with respect to the container, the label, as well as the gel appearance, smell and texture, and neither subjects, investigator, or staff working on the trial were aware of treatment allocation to the double-blind treatment groups. In the single-blind arm with Voltaren gel four times a day (QID), Gel tubes were masked to fully cover any branding information.

Arms

Are arms mutually exclusive?	Yes
Arm title	AMZ001 twice daily (BID)

Arm description:

AMZ001 gel twice daily

Arm type	Experimental
Investigational medicinal product name	AMZ001 gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Gel application

Arm title	AMZ001 once daily (QD)

Arm description:

AMZ001 gel once daily, Placebo gel once daily.

Arm type	Experimental
Investigational medicinal product name	AMZ001 gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Gel application

Arm title	Placebo Twice daily (BID)

Arm description:

Placebo gel twice daily.

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:

Placebo gel application.

Arm title	Voltaren Gel four times a day (QID)

Arm description:

Voltaren gel 1% applied 4 times a day.

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

Dosage and administration details:

Voltaren gel 1% 4 times a day.

Number of subjects in period 1	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)
Started	121	121	121
Completed	114	109	108
Not completed	7	12	13
Consent withdrawn by subject	1	1	2
Physician decision	-	1	-
Adverse event, non-fatal	3	8	7
Lost to follow-up	2	-	-
Lack of efficacy	1	2	2
Protocol deviation	-	-	2

Number of subjects in period 1	Voltaren Gel four times a day (QID)
Started	81
Completed	70
Not completed	11
Consent withdrawn by subject	2
Physician decision	-
Adverse event, non-fatal	5
Lost to follow-up	2
Lack of efficacy	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	AMZ001 twice daily (BID)
Reporting group description:	
AMZ001 gel twice daily	
Reporting group title	AMZ001 once daily (QD)
Reporting group description:	
AMZ001 gel once daily, Placebo gel once daily.	
Reporting group title	Placebo Twice daily (BID)
Reporting group description:	
Placebo gel twice daily.	
Reporting group title	Voltaren Gel four times a day (QID)
Reporting group description:	
Voltaren gel 1% applied 4 times a day.	

Reporting group values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)
Number of subjects	121	121	121
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)	60	55	62
From 65-84 years	61	66	59
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	83	83	77
Male	38	38	44

Reporting group values	Voltaren Gel four times a day (QID)	Total	
Number of subjects	81	444	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	39	216	

From 65-84 years	41	227	
85 years and over	1	1	

Gender categorical Units: Subjects			
Female	54	297	
Male	27	147	

End points

End points reporting groups

Reporting group title	AMZ001 twice daily (BID)
Reporting group description: AMZ001 gel twice daily	
Reporting group title	AMZ001 once daily (QD)
Reporting group description: AMZ001 gel once daily, Placebo gel once daily.	
Reporting group title	Placebo Twice daily (BID)
Reporting group description: Placebo gel twice daily.	
Reporting group title	Voltaren Gel four times a day (QID)
Reporting group description: Voltaren gel 1% applied 4 times a day.	

Primary: WOMAC pain Sub-score

End point title	WOMAC pain Sub-score[1]

End point description:

Change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain sub-score (questions 1-5; score 0 [no pain]-50 [extreme pain]) on target knee (double-blind treatment group only). The WOMAC pain sub-score was normalised to a 0-100 point scale for data analysis.

End point type	Primary

End point timeframe:

Baseline, Week 4.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	120	120	
Units: Score on a scale				
least squares mean (confidence interval 95%)	-26.49 (-29.6 to -23.38)	-27.33 (-30.5 to -24.17)	-22.73 (-25.9 to -19.55)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo

Statistical analysis description:

MMRM ANCOVA

Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)

Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0969
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.21
upper limit	0.68

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA.	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.09
upper limit	-0.12

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v AMZ001 once daily (QD)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7098
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	5.28

Secondary: WOMAC Total Score

End point title	WOMAC Total Score[2]

End point description:

Change from baseline in WOMAC total score (double-blind treatment group only). The WOMAC total score was normalised to a 0-100 point scale for data analysis.

End point type	Secondary

End point timeframe:

Baseline, week 4.

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	120	120	
Units: score on a scale.				
least squares mean (confidence interval 95%)	-24.15 (-26.95 to -21.34)	-23.32 (-26.16 to -20.47)	-20.57 (-23.42 to -17.72)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo

Statistical analysis description:

MMRM ANCOVA.

Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0789
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.58
upper limit	0.42

Statistical analysis title	AMZ001 QD Treatment difference vs placebo

Statistical analysis description:

MMRM ANCOVA.

Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)

Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1802
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.78
upper limit	1.28

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description:	
MMRM ANCOVA.	
Comparison groups	AMZ001 once daily (QD) v AMZ001 twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6837
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.83
upper limit	3.17

Secondary: WOMAC function score

End point title	WOMAC function score[3]

End point description:

Change from baseline in WOMAC function score (double-blind treatment group only). The WOMAC function score was normalised to a 0-100 point scale for data analysis.

End point type	Secondary

End point timeframe:

Baseline, week 4. Change from baseline in WOMAC function csore (double-blind treatment group only).

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	120	120	
Units: Score on a scale				
least squares mean (confidence interval 95%)	-23.43 (-26.29 to -20.58)	-22.30 (-25.19 to -19.40)	-19.94 (-22.84 to -17.04)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA.	
Comparison groups	Placebo Twice daily (BID) v AMZ001 twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0921
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.57
upper limit	0.57

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2593
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.46
upper limit	1.74

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description: MMRM ANCOVA.	

Comparison groups	AMZ001 once daily (QD) v AMZ001 twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5834
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.21
upper limit	2.93

Secondary: WOMAC stiffness

End point title	WOMAC stiffness[4]

End point description:

Change from baseline in WOMAC stiffness score (double-blind treatment group only). The WOMAC stiffness score was normalised to a 0-100 point scale for data analysis.

End point type	Secondary

End point timeframe:

Baseline, week 4.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	120	120	
Units: score on a scale.				
least squares mean (confidence interval 95%)	-23.17 (-26.42 to -19.93)	-23.35 (-26.66 to -20.05)	-20.65 (-23.96 to -17.34)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo

Statistical analysis description:

MMRM ANCOVA.

Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2854
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.52

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.16
upper limit	2.11

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA.	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2567
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.38
upper limit	1.97

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v AMZ001 once daily (QD)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9394
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.45
upper limit	4.81

Secondary: WOMAC pain weight-bearing score

End point title	WOMAC pain weight-bearing score[5]

End point description:

Changes from baseline in the WOMAC pain weight-bearing score (questions 1, 2 and 5) (double-blind

treatment groups only). The WOMAC pain weight-bearing score was normalised to a 0-100 point scale for data analysis.

End point type	Secondary

End point timeframe:

Baseline, week 4.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	120	120	
Units: score on a scale				
least squares mean (confidence interval 95%)	-27.03 (-30.36 to -23.70)	-27.68 (-31.07 to -24.30)	-22.65 (-26.04 to -19.25)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo

Statistical analysis description:

MMRM ANCOVA

Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.071
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-4.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.14
upper limit	0.38

Statistical analysis title	AMZ001 QD Treatment difference vs placebo

Statistical analysis description:

MMRM ANCOVA.

Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0396
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.83
upper limit	-0.24

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description:	
MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v AMZ001 once daily (QD)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7877
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	5.4

Secondary: WOMAC pain non-weight-bearing score

End point title	WOMAC pain non-weight-bearing score[6]

End point description:

Changes from baseline in the WOMAC pain non-weight-bearing score (questions 1, 2 and 5) (double-blind treatment groups only). The WOMAC pain non-weight-bearing score was normalised to a 0-100 point scale for data analysis.

End point type	Secondary

End point timeframe:

Baseline, week 4.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	120	120	
Units: score on a scale				
least squares mean (confidence interval 95%)	-25.65 (-28.87 to -22.44)	-26.89 (-30.17 to -23.61)	-22.93 (-26.22 to -19.65)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	Placebo Twice daily (BID) v AMZ001 twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.246
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.32
upper limit	1.88

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0944
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.6
upper limit	0.68

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Comparison groups	AMZ001 once daily (QD) v AMZ001 twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5961
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.35
upper limit	5.83

Secondary: ICOAP total score

End point title	ICOAP total score[7]

End point description:

Change from baseline in total Intermittent and Constant Osteoarthritis Pain (ICOAP) scores (score 0 [no pain]- 4 [extreme pain]) (double-blind treatment group only). ICOAP scores were normalized to a 0-100-point scale for the analysis.

End point type	Secondary

End point timeframe:

Baseline, week 4

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	120	120	
Units: score on a scale				
least squares mean (confidence interval 95%)	-20.62 (-23.40 to -17.84)	-18.87 (-21.72 to -16.02)	-17.98 (-20.83 to -15.13)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo

Statistical analysis description:

MMRM ANCOVA

Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1941
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.62
upper limit	1.35

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.664
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.92
upper limit	3.14

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v AMZ001 twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3896
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.73
upper limit	2.24

Secondary: ICOAP constant pain score

End point title	ICOAP constant pain score[8]
End point description: Change from baseline in total Intermittent and Constant Osteoarthritis Pain (ICOAP) scores (score 0 [no pain]- 4 [extreme pain]) (double-blind treatment group only) .ICOAP scores were normalized to a 0-100-point scale for the analysis.	
End point type	Secondary
End point timeframe: Baseline, week 4	

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	120	120	
Units: score on a scale				
least squares mean (confidence interval 95%)	-20.82 (-23.91 to -17.73)	-19.01 (-22.18 to -15.83)	-18.37 (-21.54 to -15.19)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2784
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.88
upper limit	1.98

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7808
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.13
upper limit	3.86

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description:	
MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v AMZ001 once daily (QD)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4222
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.25
upper limit	2.62

Secondary: ICOAP intermittent pain score

End point title	ICOAP intermittent pain score[9]
End point description:	
Change from baseline in total Intermittent and Constant Osteoarthritis Pain (ICOAP) scores (score 0 [no pain]- 4 [extreme pain]) (double-blind treatment group only) .ICOAP scores were normalized to a 0-100-point scale for the analysis.	
End point type	Secondary
End point timeframe:	
Baseline, week 4.	

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	120	120	
Units: score on a scale				
least squares mean (confidence interval 95%)	-20.18 (-23.19 to -17.17)	-19.00 (-22.09 to -15.92)	-17.99 (-21.08 to -14.90)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo
Statistical analysis description:	
MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)

Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3202
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.51
upper limit	2.13

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6496
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.38
upper limit	3.36

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v AMZ001 once daily (QD)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5926
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.49
upper limit	3.14

Secondary: Chair-stand test

End point title	Chair-stand test[10]

End point description:

Physical function assessed by the Chair-stand test. Change from baseline in physical function assessed by the chair-stand test.

End point type	Secondary

End point timeframe:

baseline, week 4

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	120	120	
Units: number of repetitions				
least squares mean (confidence interval 95%)	2.41 (1.98 to 2.83)	2.30 (1.87 to 2.72)	2.37 (1.94 to 2.80)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo

Statistical analysis description:

MMRM ANCOVA

Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9051
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	0.64

Statistical analysis title	AMZ001 QD Treatment difference vs placebo

Statistical analysis description:

MMRM ANCOVA

Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)

Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8049
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	0.53

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Comparison groups	AMZ001 twice daily (BID) v AMZ001 once daily (QD)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7126
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	0.71

Secondary: OMERACT-OARSI responder rate

End point title	OMERACT-OARSI responder rate[11]

End point description:

OMERACT-OARSI (Outcome Measures in Rheumatology- Osteoarthritis Research Society International) responder rate (double-blind treatment group only)

End point type	Secondary

End point timeframe:

Week 4

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	109	109	
Units: none				
number (confidence interval 95%)	0.765 (0.679 to 0.834)	0.826 (0.743 to 0.886)	0.725 (0.634 to 0.800)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4876
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	1.238
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.678
upper limit	2.26

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0763
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.799
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	3.443

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD

Statistical analysis description:	
MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v AMZ001 once daily (QD)
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2642
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.688
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.357
upper limit	1.326

Secondary: Total dose of rescue medication

End point title	Total dose of rescue medication[12]
End point description:	
Total dose of rescue medication calculated as the average gram use/day, based on pill counts (double-blind treatment group only).	
End point type	Secondary
End point timeframe:	
week 1 through week 4	

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	120	120	
Units: g/day				
least squares mean (confidence interval 95%)	0.27 (0.19 to 0.36)	0.31 (0.22 to 0.40)	0.30 (0.21 to 0.39)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo
Statistical analysis description:	
MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)

Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6432
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.1

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9351
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.13

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v AMZ001 once daily (QD)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5859
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.09

Secondary: Time between baseline and first use of rescue medication

End point title	Time between baseline and first use of rescue medication[13]

End point description:

Time between baseline and first use of rescue medication (double-blind treatment group only)

End point type	Secondary

End point timeframe:

week 1 through week 4

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	120	120	
Units: days				
median (confidence interval 95%)	17 (7 to 24)	9 (5 to 15)	10 (4 to 17)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo
Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1248
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.07

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)

Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4136
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.2

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Comparison groups	AMZ001 once daily (QD) v AMZ001 twice daily (BID)
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4618
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.22

Secondary: Impact of Osteoarthritis on daily living (PGA score)

End point title	Impact of Osteoarthritis on daily living (PGA score)[14]

End point description:

Changes from baseline in the impact of osteoarthritis on daily living as assessed by the Patient Global Assessment (PGA) score (0 [none] - 10 [extreme]) (double-blind treatment group only)

End point type	Secondary

End point timeframe:

Baseline, week 4

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	120	120	
Units: score on a scale				
least squares mean (confidence interval 95%)	-2.29 (-2.63 to -1.94)	-2.31 (-2.66 to -1.96)	-1.68 (-2.03 to -1.32)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0162
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.11
upper limit	-0.11

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0134
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	-0.13

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD

Comparison groups	AMZ001 twice daily (BID) v AMZ001 once daily (QD)
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9321
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.52

Secondary: WPAI % time missed

End point title	WPAI % time missed[15]

End point description:

Changes from baseline in the percentage of work time missed due to health, assessed by the Work Productivity and Active Impairment (WPAI scores 0-100% in four different categories: absenteeism, presenteeism, work productivity loss, and activity impairment). It was determined only for subjects currently employed (doubleblind treatment group only)

End point type	Secondary

End point timeframe:

Baseline, week 4

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	41	39	
Units: percentage time				
least squares mean (confidence interval 95%)	0.39 (-2.73 to 3.51)	-3.10 (-6.43 to 0.23)	1.58 (-2.01 to 5.16)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo

Statistical analysis description:

MMRM ANCOVA

Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6228
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.95
upper limit	3.57

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0612
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.58
upper limit	0.22

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v AMZ001 once daily (QD)
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1345
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	8.06

Secondary: WPAI % impairment while working

End point title	WPAI % impairment while working[16]

End point description:

Changes from baseline in the degree that health affected productivity while working expressed as a percentage, assessed by the Work Productivity and Active Impairment (WPAI scores 0-100% in four different categories: absenteeism, presenteeism, work productivity loss, and activity impairment). It was determined only for subjects currently employed (doubleblind treatment group only)

End point type	Secondary

End point timeframe:

Baseline, week 4

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	47	39	
Units: percentage				
least squares mean (confidence interval 95%)	-13.11 (-18.71 to -7.51)	-14.38 (-20.57 to -8.19)	-5.28 (-12.26 to 1.70)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo

Statistical analysis description:

MMRM ANCOVA

Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0876
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.81
upper limit	1.16

Statistical analysis title	AMZ001 QD Treatment difference vs placebo

Statistical analysis description:	
MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0555
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.42
upper limit	0.22

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description:	
MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v AMZ001 twice daily (BID)
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7648
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.11
upper limit	9.66

Secondary: WPAI % overall work impairment

End point title	WPAI % overall work impairment[17]

End point description:

Changes from baseline in the percentage of overall work impairment due to health, assessed by the Work Productivity and Active Impairment (WPAI scores 0-100% in four different categories: absenteeism, presenteeism, work productivity loss, and activity impairment). It was determined only for subjects currently employed (doubleblind treatment group only).

End point type	Secondary

End point timeframe:

Baseline, week 4

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	39	34	
Units: percentage				
least squares mean (confidence interval 95%)	-11.69 (-17.95 to -5.43)	-16.93 (-23.95 to -9.91)	-6.50 (-14.19 to 1.20)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3054
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.17
upper limit	4.77

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0492
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-10.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.84
upper limit	-0.04

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD

Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2752
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	14.68

Secondary: WPAI % activity impairment

End point title	WPAI % activity impairment[18]

End point description:

Changes from baseline in the the degree that health affected regular activities expressed as a percentage, assessed by the Work Productivity and Active Impairment (WPAI scores 0-100% in four different categories: absenteeism, presenteesism, work productivity loss, and activity impairment). It was determined only for subjects currently employed (doubleblind treatment group only).

End point type	Secondary

End point timeframe:

Baseline, week 4

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	120	120	
Units: percentage				
least squares mean (confidence interval 95%)	-17.75 (-21.45 to -14.06)	-20.41 (-24.15 to -16.68)	-13.03 (-16.79 to -9.27)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo

Statistical analysis description:

MMRM ANCOVA

Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)

Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10
upper limit	0.55

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0064
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.69
upper limit	-2.08

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v AMZ001 once daily (QD)
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3202
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.59
upper limit	7.92

Secondary: EQ-5D VAS score

End point title	EQ-5D VAS score[19]

End point description:

Changes from baseline in quality of life assessed by the EQ5D (score 0 [extremely poor] -100 [great] mm on a visual analogue scale) (double-blind treatment group only)

End point type	Secondary

End point timeframe:

Baseline, week 4

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	120	120	
Units: score on a scale				
least squares mean (confidence interval 95%)	13.04 (10.13 to 15.94)	11.76 (8.82 to 14.71)	8.34 (5.39 to 11.28)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo

Statistical analysis description:

MMRM ANCOVA

Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0264
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	8.85

Statistical analysis title	AMZ001 QD Treatment difference vs placebo

Statistical analysis description:

MMRM ANCOVA

Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)

Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1072
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	7.6

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description:	
MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5459
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.86
upper limit	5.41

Other pre-specified: Skin Reactions (Skin Tolerability assessment)	
End point title	Skin Reactions (Skin Tolerability assessment)
End point description:	
Nature, incidence and severity of skin reactions on the application site.	
End point type	Other pre-specified
End point timeframe:	
Week 4.	

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	Voltaren Gel four times a day (QID)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	121	121	121	81
Units: number of events				
Normal skin; no erythema	100	89	79	68
Questionable erythema not covering entire applicat	14	18	20	3
Definite erythema covering entire application site	2	2	10	0
Definite erythema and swelling or induration	0	0	0	0
Blister formation and/or necrosis	0	0	0	1
Not done	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Post-hoc: WOMAC pain Sub-score (subgroup with WOMAC normalized pain sub-score ≥40 at baseline)

End point title	WOMAC pain Sub-score (subgroup with WOMAC normalized pain sub-score ≥40 at baseline)[20]

End point description:

Change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain sub-score (questions 1-5; score 0 [no pain]-50 [extreme pain]) on target knee (sub-group of subjects meeting the WOMAC pain sub-score inclusion criterion at both screening and baseline). The WOMAC pain sub-score was normalised to a 0-100 point scale for data analysis.

End point type	Post-hoc

End point timeframe:

Baseline, week 4.

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	107	106	
Units: score on a scale.				
least squares mean (confidence interval 95%)	-28.54 (-31.87 to -25.20)	-29.02 (-32.45 to -25.60)	-23.18 (-26.64 to -19.72)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo

Statistical analysis description:

MMRM ANCOVA.

Comparison groups	Placebo Twice daily (BID) v AMZ001 twice daily (BID)
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0292
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-5.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.16
upper limit	-0.54

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	213
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0189
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-5.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.71
upper limit	-0.97

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v AMZ001 once daily (QD)
Number of subjects included in analysis	216
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.841
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.49

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	5.27

Post-hoc: WOMAC Total Score (subgroup with WOMAC normalized pain sub-score ≥40 at baseline)

End point title	WOMAC Total Score (subgroup with WOMAC normalized pain sub-score ≥40 at baseline)[21]

End point description:

Change from baseline in WOMAC total score (sub-group of subjects meeting the WOMAC pain sub-score inclusion criterion at both screening and baseline). The WOMAC total score was normalised to a 0-100 point scale for data analysis.

End point type	Post-hoc

End point timeframe:

Baseline, week 4.

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	107	106	
Units: score on a scale.				
least squares mean (confidence interval 95%)	-25.54 (-28.54 to -22.54)	-24.03 (-27.11 to -20.95)	-20.61 (-23.71 to -17.51)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo

Statistical analysis description:

MMRM ANCOVA.

Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)
Number of subjects included in analysis	215
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0252
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.24
upper limit	-0.62

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	213
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.125
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.79
upper limit	0.95

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 twice daily (BID) v AMZ001 once daily (QD)
Number of subjects included in analysis	216
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4912
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.81
upper limit	2.79

Post-hoc: WOMAC function score (subgroup with WOMAC normalized pain sub-score ≥40 at baseline)

End point title	WOMAC function score (subgroup with WOMAC normalized pain sub-score ≥40 at baseline)[22]

End point description:

Change from baseline in WOMAC function score (sub-group of subjects meeting the WOMAC pain sub-score inclusion criterion at both screening and baseline). The WOMAC total score was normalised to a 0-100 point scale for data analysis.

End point type	Post-hoc

End point timeframe:

Baseline, week 4.

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	107	106	
Units: score on a scale				
least squares mean (confidence interval 95%)	-24.69 (-27.75 to -21.64)	-22.84 (-25.97 to -19.70)	-19.84 (-23.00 to -16.68)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA.	
Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)
Number of subjects included in analysis	215
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0306
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.24
upper limit	-0.45

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA.	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	213
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.1879
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.99

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.45
upper limit	1.47

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description:	
MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v AMZ001 twice daily (BID)
Number of subjects included in analysis	216
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4059
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.24
upper limit	2.53

Post-hoc: WOMAC stiffness (subgroup with WOMAC normalized pain sub-score ≥40 at baseline)

End point title	WOMAC stiffness (subgroup with WOMAC normalized pain sub-score ≥40 at baseline)[23]

End point description:

Change from baseline in WOMAC stiffness score (sub-group of subjects meeting the WOMAC pain sub-score inclusion criterion at both screening and baseline). The WOMAC stiffness score was normalised to a 0-100 point scale for data analysis.

End point type	Post-hoc

End point timeframe:

Baseline, week 4.

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Voltaren gel arm is an exploratory arm and exploratory endpoints results are not reported.

End point values	AMZ001 twice daily (BID)	AMZ001 once daily (QD)	Placebo Twice daily (BID)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	107	106	
Units: score on scale				
least squares mean (confidence interval 95%)	-24.08 (-27.52 to -20.64)	-23.57 (-27.11 to -20.03)	-20.33 (-23.89 to -16.76)	

Statistical analyses

Statistical analysis title	AMZ001 BID treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA.	
Comparison groups	AMZ001 twice daily (BID) v Placebo Twice daily (BID)
Number of subjects included in analysis	215
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.1374
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.71
upper limit	1.2

Statistical analysis title	AMZ001 QD Treatment difference vs placebo
Statistical analysis description: MMRM ANCOVA	
Comparison groups	AMZ001 once daily (QD) v Placebo Twice daily (BID)
Number of subjects included in analysis	213
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.2058
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-3.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.27
upper limit	1.79

Statistical analysis title	AMZ001 BID Treatment difference vs AMZ001 QD
Statistical analysis description: MMRM ANCOVA.	
Comparison groups	AMZ001 once daily (QD) v AMZ001 twice daily (BID)

Number of subjects included in analysis	216
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.8388
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.45
upper limit	4.43

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Informed Consent signature to safety follow-up phone call.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	AMZ001 BID
Reporting group description: -	
Reporting group title	AMZ001 QD
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Voltaren Gel 1%
Reporting group description: -	

Serious adverse events	AMZ001 BID	AMZ001 QD	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 121 (0.00%)	0 / 121 (0.00%)	0 / 121 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Voltaren Gel 1%		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 81 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	AMZ001 BID	AMZ001 QD	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 121 (34.71%)	40 / 121 (33.06%)	76 / 121 (62.81%)
Nervous system disorders			

Headache			
subjects affected / exposed	2 / 121 (1.65%)	1 / 121 (0.83%)	8 / 121 (6.61%)
occurrences (all)	3	2	9
General disorders and administration site conditions			
Application site dryness			
subjects affected / exposed	18 / 121 (14.88%)	13 / 121 (10.74%)	16 / 121 (13.22%)
occurrences (all)	18	13	16
Application site pruritus			
subjects affected / exposed	5 / 121 (4.13%)	8 / 121 (6.61%)	6 / 121 (4.96%)
occurrences (all)	5	8	6
Application site erythema			
subjects affected / exposed	11 / 121 (9.09%)	15 / 121 (12.40%)	40 / 121 (33.06%)
occurrences (all)	12	16	41
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 121 (4.96%)	3 / 121 (2.48%)	6 / 121 (4.96%)
occurrences (all)	7	3	6

Non-serious adverse events	Voltaren Gel 1%		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 81 (18.52%)		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Application site dryness			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	5		
Application site pruritus			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	3		
Application site erythema			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	4		
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 81 (4.94%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2018	Updates and corrections
22 November 2018	Updates

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported