



Clinical trial results:

A Phase 2a Study Evaluating the Safety, Efficacy, and Pharmacodynamic Effects of ABT-981 in Patients with Knee Osteoarthritis

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2013-003467-60 |
| Trial protocol | DK GB NL ES IT |
| Global end of trial date | 13 December 2016 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 |
| This version publication date | 10 July 2019 |
| First version publication date | 06 December 2017 |
| Version creation reason | • Correction of full data set correct values in two endpoint descriptions |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | M13-741 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02087904 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | AbbVie Deutschland GmbH & Co.KG |
| Sponsor organisation address | AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB |
| Public contact | Marc Levesque, MD, Abbvie, 1 847-936-7855, marc.levesque@abbvie.com |
| Scientific contact | Marc Levesque, MD, Abbvie, 1 847-936-7855, marc.levesque@abbvie.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 | 13 December 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 December 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of ABT-981 on osteoarthritis (OA) knee pain using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at Week 16 and synovitis/effusion volume of the index knee using quantitative measures and semi-quantitative magnetic resonance imaging (MRI) scoring at Week 26 in subjects with knee osteoarthritis.

Protection of trial subjects:

Participant and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 04 June 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Spain: 58 |
| Country: Number of subjects enrolled | Netherlands: 2 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | Denmark: 61 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Italy: 3 |
| Country: Number of subjects enrolled | Australia: 3 |
| Country: Number of subjects enrolled | Canada: 33 |
| Country: Number of subjects enrolled | Mexico: 31 |
| Country: Number of subjects enrolled | Puerto Rico: 5 |
| Country: Number of subjects enrolled | United States: 150 |
| Worldwide total number of subjects | 350 |
| EEA total number of subjects | 128 |

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) | 219 |
| From 65 to 84 years | 131 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study included a screening period (approximately 45 days prior to first study drug dose) and a washout period (5 half-lives of the longest acting analgesic used, or 48 hours, whichever was longer, in which all standard of care analgesic medications were discontinued prior to the first study drug dose).

Pre-assignment period milestones

| | |
|----------------------------|-----|
| Number of subjects started | 350 |
|----------------------------|-----|

| | |
|------------------------------|-----|
| Number of subjects completed | 347 |
|------------------------------|-----|

Pre-assignment subject non-completion reasons

| | |
|----------------------------|-------------------------------|
| Reason: Number of subjects | did not receive study drug: 3 |
|----------------------------|-------------------------------|

Period 1

| | |
|----------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
|----------------|--------------------------------|

| | |
|------------------------------|-----|
| Is this the baseline period? | Yes |
|------------------------------|-----|

| | |
|-------------------|-------------------------|
| Allocation method | Randomised - controlled |
|-------------------|-------------------------|

| | |
|---------------|--------------|
| Blinding used | Double blind |
|---------------|--------------|

| | |
|---------------|--|
| Roles blinded | Investigator, Carer, Assessor, Subject |
|---------------|--|

Blinding implementation details:

The study was conducted in a double-blind manner such that the investigator and subjects were blinded to the treatment assignments. All clinical site personnel, except for the unblinded licensed pharmacist or unblinded, qualified pharmacy technician and an unblinded monitor, remained blinded to the treatment.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|-----------|---------|
| Arm title | Placebo |
|-----------|---------|

Arm description:

Matching placebo SC E2W

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|---------|
| Investigational medicinal product name | placebo |
|--|---------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|----------------------|
| Pharmaceutical forms | Powder for injection |
|----------------------|----------------------|

| | |
|--------------------------|------------------|
| Routes of administration | Subcutaneous use |
|--------------------------|------------------|

Dosage and administration details:

Study drug (placebo) was provided as a lyophilized powder in vials that were reconstituted to a solution for injection at the clinical site by the unblinded pharmacist or unblinded, qualified designees as permitted by local/state law.

| | |
|-----------|---------------|
| Arm title | ABT-981 25 mg |
|-----------|---------------|

Arm description:

25 mg ABT-981 SC E2W

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|----------------------|
| Investigational medicinal product name | ABT-981 |
| Investigational medicinal product code | |
| Other name | lutikizumab |
| Pharmaceutical forms | Powder for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Study drug (ABT-981) was provided as a lyophilized powder in vials that were reconstituted to a solution for injection at the clinical site by the unblinded pharmacist or unblinded, qualified designees as permitted by local/state law.

| | |
|------------------|----------------|
| Arm title | ABT-981 100 mg |
|------------------|----------------|

Arm description:

100 mg ABT-981 SC E2W

| | |
|--|----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ABT-981 |
| Investigational medicinal product code | |
| Other name | lutikizumab |
| Pharmaceutical forms | Powder for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Study drug (ABT-981) was provided as a lyophilized powder in vials that were reconstituted to a solution for injection at the clinical site by the unblinded pharmacist or unblinded, qualified designees as permitted by local/state law.

| | |
|------------------|----------------|
| Arm title | ABT-981 200 mg |
|------------------|----------------|

Arm description:

200 mg ABT-981 SC E2W

| | |
|--|----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ABT-981 |
| Investigational medicinal product code | |
| Other name | lutikizumab |
| Pharmaceutical forms | Powder for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Study drug (ABT-981) was provided as a lyophilized powder in vials that were reconstituted to a solution for injection at the clinical site by the unblinded pharmacist or unblinded, qualified designees as permitted by local/state law.

| Number of subjects in period 1^[1] | Placebo | ABT-981 25 mg | ABT-981 100 mg |
|---|---------|---------------|----------------|
| Started | 85 | 89 | 85 |
| Completed | 60 | 70 | 65 |
| Not completed | 25 | 19 | 20 |
| Consent withdrawn by subject | 8 | 3 | 7 |
| Not specified | 6 | 2 | 4 |
| Adverse event | 8 | 4 | 4 |
| Lost to follow-up | - | 4 | 2 |
| Lack of efficacy | 3 | 6 | 3 |

| Number of subjects in period 1^[1] | ABT-981 200 mg |
|---|----------------|
| Started | 88 |
| Completed | 64 |
| Not completed | 24 |
| Consent withdrawn by subject | 4 |
| Not specified | 4 |
| Adverse event | 12 |
| Lost to follow-up | 2 |
| Lack of efficacy | 2 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Three subjects did not receive study drug.

Baseline characteristics

Reporting groups

| | |
|---|----------------|
| Reporting group title | Placebo |
| Reporting group description: Matching placebo SC E2W | |
| Reporting group title | ABT-981 25 mg |
| Reporting group description: 25 mg ABT-981 SC E2W | |
| Reporting group title | ABT-981 100 mg |
| Reporting group description: 100 mg ABT-981 SC E2W | |
| Reporting group title | ABT-981 200 mg |
| Reporting group description: 200 mg ABT-981 SC E2W | |

| Reporting group values | Placebo | ABT-981 25 mg | ABT-981 100 mg |
|------------------------------------|---------|---------------|----------------|
| Number of subjects | 85 | 89 | 85 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|------------------|------------------|------------------|
| Age continuous Units: years arithmetic mean standard deviation | 59.53 ± 8.850 | 61.63 ± 7.546 | 60.21 ± 8.194 |
| Gender categorical Units: Subjects | | | |
| Female | 52 | 63 | 53 |
| Male | 33 | 26 | 32 |

| Reporting group values | ABT-981 200 mg | Total | |
|------------------------------------|----------------|-------|--|
| Number of subjects | 88 | 347 | |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-------------------|-----|--|
| Age continuous Units: years arithmetic mean standard deviation | 59.05 ± 10.273 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 57 | 225 | |
| Male | 31 | 122 | |

End points

End points reporting groups

| | |
|------------------------------|----------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching placebo SC E2W | |
| Reporting group title | ABT-981 25 mg |
| Reporting group description: | |
| 25 mg ABT-981 SC E2W | |
| Reporting group title | ABT-981 100 mg |
| Reporting group description: | |
| 100 mg ABT-981 SC E2W | |
| Reporting group title | ABT-981 200 mg |
| Reporting group description: | |
| 200 mg ABT-981 SC E2W | |

Primary: Change from Baseline in WOMAC Pain Scores of the Index Knee at Week 16

| | |
|---|--|
| End point title | Change from Baseline in WOMAC Pain Scores of the Index Knee at Week 16 |
| End point description: | |
| <p>The WOMAC was developed to assess pain, stiffness, and physical function in subjects with hip and/or knee osteoarthritis. The WOMAC consists of 24 items divided into 3 subscales: Pain (5 items); Stiffness (2 items); and Physical Function (17 items). Each item is rated on an 11-point (0 to 10) numerical rating scale (NRS). The pain sub-score has a range of 0 (no pain) to 50 (maximum pain). A negative change from baseline indicates improvement.</p> | |
| <p>Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, LOCF (missing responses were imputed by calculation based on the last non-missing post-baseline component values).</p> | |
| End point type | Primary |
| End point timeframe: | |
| Baseline, Week 16 | |

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|------------------------|------------------------|-------------------------|-------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 85 | 88 | 84 | 88 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -8.9 (-10.96 to -6.90) | -9.2 (-11.23 to -7.23) | -11.8 (-13.84 to -9.75) | -10.1 (-12.10 to -8.10) |

Statistical analyses

| | |
|----------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v ABT-981 25 mg |

| | |
|---|------------------------|
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.834 ^[1] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.13 |
| upper limit | 2.53 |

Notes:

[1] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and Kellgren-Lawrence (K-L) grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.05 ^[2] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.73 |
| upper limit | 0.01 |

Notes:

[2] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.415 ^[3] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4 |
| upper limit | 1.66 |

Notes:

[3] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Primary: Change from Baseline in Quantitative Synovitis of the Index Knee at Week 26

| | |
|---|---|
| End point title | Change from Baseline in Quantitative Synovitis of the Index Knee at Week 26 |
| End point description: Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases. | |
| End point type | Primary |
| End point timeframe: Baseline, Week 26 | |

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|-------------------------|------------------------|--------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 59 | 65 | 59 | 63 |
| Units: mm | | | | |
| least squares mean (confidence interval 95%) | -0.05 (-0.107 to 0.011) | 0.01 (-0.045 to 0.068) | -0.08 (-0.134 to -0.016) | 0.01 (-0.047 to 0.067) |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.145 ^[4] |
| Method | ANCOVA |
| Parameter estimate | LS |
| Point estimate | 0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.021 |
| upper limit | 0.141 |

Notes:

[4] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|----------------------------|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v ABT-981 100 mg |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.52 ^[5] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.11 |
| upper limit | 0.056 |

Notes:

[5] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 122 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.159 ^[6] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.023 |
| upper limit | 0.139 |

Notes:

[6] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Primary: Change from Baseline in Effusion Volume of the Index Knee at Week 26

| | |
|---|--|
| End point title | Change from Baseline in Effusion Volume of the Index Knee at Week 26 |
| End point description: | |
| Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline, Week 26 | |

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|------------------------|------------------------|-------------------------|-------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 69 | 67 | 68 |
| Units: mL | | | | |
| least squares mean (confidence interval 95%) | 0.03 (-2.498 to 2.562) | 0.26 (-2.113 to 2.624) | -1.04 (-3.421 to 1.347) | -1.49 (-3.868 to 0.898) |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|-------------------------|
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 129 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.897 ^[7] |
| Method | ANCOVA |
| Parameter estimate | LS mean Difference |
| Point estimate | 0.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.193 |
| upper limit | 3.642 |

Notes:

[7] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| Statistical analysis title | Statistical Analysis 2 |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.542 ^[8] |
| Method | ANCOVA |
| Parameter estimate | LS mean Difference |
| Point estimate | -1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.515 |
| upper limit | 2.377 |

Notes:

[8] - P-value for test of difference between ABT-981 100 dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| Statistical analysis title | Statistical Analysis 3 |
|----------------------------|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |

| | |
|---|------------------------|
| Number of subjects included in analysis | 128 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.385 ^[9] |
| Method | ANCOVA |
| Parameter estimate | LS mean Difference |
| Point estimate | -1.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.95 |
| upper limit | 1.916 |

Notes:

[9] - P-value for test of difference between ABT-981 200 dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Primary: Change from Baseline in Whole-Organ Magnetic Resonance Imaging Score (WORMS) Semi-Quantitative Synovitis/Effusion Score of the Index Knee at Week 26

| | |
|-----------------|--|
| End point title | Change from Baseline in Whole-Organ Magnetic Resonance Imaging Score (WORMS) Semi-Quantitative Synovitis/Effusion Score of the Index Knee at Week 26 |
|-----------------|--|

End point description:

Semi-quantitative synovitis/effusion volume WORMS scores were scored as normal (0), < 33% of maximum estimated distention (1), 33% – 66% of maximum estimated distention (2), or > 66% of maximum estimated distention (3).

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Week 26

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 70 | 76 | 70 | 75 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | 0.07 (-0.057 to 0.193) | -0.01 (-0.130 to 0.113) | -0.08 (-0.205 to 0.043) | -0.07 (-0.196 to 0.048) |

Statistical analyses

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v ABT-981 25 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 146 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.384 ^[10] |
| Method | ANCOVA |
| Parameter estimate | LS mean Difference |
| Point estimate | -0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.249 |
| upper limit | 0.096 |

Notes:

[10] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 140 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.095 ^[11] |
| Method | ANCOVA |
| Parameter estimate | LS mean Difference |
| Point estimate | -0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.324 |
| upper limit | 0.026 |

Notes:

[11] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 145 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.106 ^[12] |
| Method | ANCOVA |
| Parameter estimate | LS mean Difference |
| Point estimate | -0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.314 |
| upper limit | 0.03 |

Notes:

[12] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Secondary: Change From Baseline in WOMAC Physical Function Scores of the Index Knee at Week 16

| | |
|-----------------|---|
| End point title | Change From Baseline in WOMAC Physical Function Scores of the Index Knee at Week 16 |
|-----------------|---|

End point description:

The WOMAC was developed to assess pain, stiffness, and physical function in subjects with hip and/or knee osteoarthritis. The WOMAC consists of 24 items divided into 3 subscales: Pain (5 items); Stiffness (2 items); and Physical Function (17 items). Each item is rated on an 11-point (0 to 10) NRS. The WOMAC physical function subscale score was 0 (normal) to 170 (least physical function). A negative change from baseline indicates improvement.

Modified intent to Treat population: all subjects who received at least 1 dose of study drug, LOCF (missing responses were imputed by calculation based on the last non-missing post-baseline component values).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 16

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|--------------------------|--------------------------|--------------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 85 | 88 | 84 | 87 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -28.7 (-35.30 to -22.15) | -29.8 (-36.27 to -23.32) | -36.3 (-42.90 to -29.69) | -32.1 (-38.64 to -25.63) |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.818 ^[13] |
| Method | ANCOVA |
| Parameter estimate | LS mean Difference |
| Point estimate | -1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.22 |
| upper limit | 8.08 |

Notes:

[13] - P-value for test of difference between ABT-981 25 mg dose group and placebo at each post-baseline time point is from an ANCOVA model with treatment, age, K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.109 ^[14] |
| Method | ANCOVA |
| Parameter estimate | LS mean Difference |
| Point estimate | -7.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.83 |
| upper limit | 1.69 |

Notes:

[14] - P-value for test of difference between ABT-981 100 mg dose group and placebo at each post-baseline time point is from an ANCOVA model with treatment, age, K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.465 ^[15] |
| Method | ANCOVA |
| Parameter estimate | LS mean Difference |
| Point estimate | -3.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.58 |
| upper limit | 5.76 |

Notes:

[15] - P-value for test of difference between ABT-981 200 mg dose group and placebo at each post-baseline time point is from an ANCOVA model with treatment, age, K-L grade as the main factors and baseline as a covariate.

Secondary: Change From Baseline in WOMAC Physical Function Scores of the Index Knee at Week 26

| | |
|-----------------|---|
| End point title | Change From Baseline in WOMAC Physical Function Scores of the Index Knee at Week 26 |
|-----------------|---|

End point description:

The WOMAC was developed to assess pain, stiffness, and physical function in subjects with hip and/or knee osteoarthritis. The WOMAC consists of 24 items divided into 3 subscales: Pain (5 items); Stiffness (2 items); and Physical Function (17 items). Each item is rated on an 11-point (0 to 10) NRS. The WOMAC physical function subscale score was 0 (normal) to 170 (least physical function). A negative change from baseline indicates improvement.

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, LOCF (missing responses were imputed by calculation based on the last non-missing post-baseline component values).

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 26 | |

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|--------------------------|--------------------------|--------------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 85 | 88 | 84 | 87 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -29.7 (-36.61 to -22.75) | -31.8 (-38.62 to -24.98) | -38.9 (-45.83 to -31.92) | -36.9 (-43.71 to -30.00) |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|-------------------------|
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.666 ^[16] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.76 |
| upper limit | 7.52 |

Notes:

[16] - P-value for test of difference between ABT-981 25 mg dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment, age, K-L grade as the main factors and baseline as a covariate.

| Statistical analysis title | Statistical Analysis 2 |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.065 ^[17] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -9.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18.95 |
| upper limit | 0.56 |

Notes:

[17] - P-value for test of difference between ABT-981 100 mg dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment, age, K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.145 ^[18] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -7.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.84 |
| upper limit | 2.49 |

Notes:

[18] - P-value for test of difference between ABT-981 200 mg dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment, age, K-L grade as the main factors and baseline as a covariate.

Secondary: Change From Baseline in WOMAC Physical Function Scores of the Index Knee at Week 52

| | |
|-----------------|---|
| End point title | Change From Baseline in WOMAC Physical Function Scores of the Index Knee at Week 52 |
|-----------------|---|

End point description:

The WOMAC was developed to assess pain, stiffness, and physical function in subjects with hip and/or knee osteoarthritis. The WOMAC consists of 24 items divided into 3 subscales: Pain (5 items); Stiffness (2 items); and Physical Function (17 items). Each item is rated on an 11-point (0 to 10) NRS. The WOMAC physical function subscale score was 0 (normal) to 170 (least physical function). A negative change from baseline indicates improvement.

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, LOCF (missing responses were imputed by calculation based on the last non-missing post-baseline component values).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 52

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|--------------------------|--------------------------|--------------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 85 | 88 | 84 | 87 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -32.9 (-40.66 to -25.12) | -36.1 (-43.76 to -28.46) | -38.7 (-46.52 to -30.92) | -39.7 (-47.37 to -32.00) |

Statistical analyses

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v ABT-981 25 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.558 ^[19] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -3.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.03 |
| upper limit | 7.59 |

Notes:

[19] - P-value for test of difference between ABT-981 25 mg dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment, age, K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.295 ^[20] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -5.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.77 |
| upper limit | 5.11 |

Notes:

[20] - P-value for test of difference between ABT-981 100 mg dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment, age, K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.218 ^[21] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -6.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.63 |
| upper limit | 4.04 |

Notes:

[21] - P-value for test of difference between ABT-981 200 mg dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment, age, K-L grade as the main factors and baseline as a covariate.

Secondary: Change From Baseline in WOMAC Pain Scores of the Index Knee at Week 26

| | |
|-----------------|--|
| End point title | Change From Baseline in WOMAC Pain Scores of the Index Knee at Week 26 |
|-----------------|--|

End point description:

The WOMAC was developed to assess pain, stiffness, and physical function in subjects with hip and/or knee osteoarthritis. The WOMAC consists of 24 items divided into 3 subscales: Pain (5 items); Stiffness (2 items); and Physical Function (17 items). Each item is rated on an 11-point (0 to 10) numerical rating scale (NRS). The pain sub-score has a range of 0 (no pain) to 50 (maximum pain). A negative change from baseline indicates improvement.

Modified intent to Treat population: all subjects who received at least 1 dose of study drug, LOCF (missing responses were imputed by calculation based on the last non-missing post-baseline component values).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 26

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|------------------------|------------------------|-------------------------|-------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 85 | 88 | 84 | 88 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -9.2 (-11.29 to -7.07) | -9.8 (-11.90 to -7.75) | -11.9 (-13.99 to -9.76) | -11.6 (-13.65 to -9.51) |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.664 ^[22] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.58 |
| upper limit | 2.28 |

Notes:

[22] - P-value for test of difference between ABT-981 25 mg dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment, age, K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.075 ^[23] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.67 |
| upper limit | 0.28 |

Notes:

[23] - P-value for test of difference between ABT-981 100 mg dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment, age, K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.107 ^[24] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.33 |
| upper limit | 0.52 |

Notes:

[24] - P-value for test of difference between ABT-981 200 mg dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment, age, K-L grade as the main factors and baseline as a covariate.

Secondary: Change From Baseline in WOMAC Pain Scores of the Index Knee at Week 52

| | |
|-----------------|--|
| End point title | Change From Baseline in WOMAC Pain Scores of the Index Knee at Week 52 |
|-----------------|--|

End point description:

The WOMAC was developed to assess pain, stiffness, and physical function in subjects with hip and/or knee osteoarthritis. The WOMAC consists of 24 items divided into 3 subscales: Pain (5 items); Stiffness (2 items); and Physical Function (17 items). Each item is rated on an 11-point (0 to 10) numerical rating scale (NRS). The pain sub-score has a range of 0 (no pain) to 50 (maximum pain). A negative change from baseline indicates improvement.

Modified intent to Treat population: all subjects who received at least 1 dose of study drug, LOCF (missing responses were imputed by calculation based on the last non-missing post-baseline component values).

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 52 | |

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|-------------------------|-------------------------|-------------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 85 | 88 | 84 | 88 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -10.0 (-12.24 to -7.68) | -11.0 (-13.29 to -8.80) | -12.1 (-14.42 to -9.84) | -12.2 (-14.49 to -10.00) |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|-------------------------|
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5 ^[25] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.26 |
| upper limit | 2.08 |

Notes:

[25] - P-value for test of difference between ABT-981 25 mg dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment, age, K-L grade as the main factors and baseline as a covariate.

| Statistical analysis title | Statistical Analysis 2 |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.186 ^[26] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.39 |
| upper limit | 1.05 |

Notes:

[26] - P-value for test of difference between ABT-981 100 mg dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment, age, K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.157 ^[27] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.46 |
| upper limit | 0.88 |

Notes:

[27] - P-value for test of difference between ABT-981 200 mg dose group and placebo at each postbaseline time point is from an ANCOVA model with treatment, age, K-L grade as the main factors and baseline as a covariate.

Secondary: Change from Baseline in Global Total Bone Marrow Lesion (BML) Score of the Index Knee Magnetic Resonance Imaging (MRI) at Week 26

| | |
|-----------------|---|
| End point title | Change from Baseline in Global Total Bone Marrow Lesion (BML) Score of the Index Knee Magnetic Resonance Imaging (MRI) at Week 26 |
|-----------------|---|

End point description:

BMLs in 15 regions were measured with MRI, and graded as 0 (normal), 1 (mild; < 25% of region), 2 (moderate; 25% – 50% of region), or 3 (severe; > 50% of region). The global total BML score was the sum of the 15 component scores, and ranged from 0 (normal) to 45 (severe).

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 26 | |

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|---------------------|--------------------|----------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 69 | 76 | 69 | 75 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | 0.1 (-0.24 to 0.43) | 0.3 (0.01 to 0.65) | -0.0 (-0.37 to 0.29) | 0.1 (-0.22 to 0.43) |

Statistical analyses

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | ABT-981 25 mg v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 145 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.319 ^[28] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.23 |
| upper limit | 0.69 |

Notes:

[28] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 138 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.564 ^[29] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 0.33 |

Notes:

[29] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 144 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.966 ^[30] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.45 |
| upper limit | 0.47 |

Notes:

[30] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Secondary: Change from Baseline in Global Total BML Score of the Index Knee MRI at Week 52

| | |
|-----------------|---|
| End point title | Change from Baseline in Global Total BML Score of the Index Knee MRI at Week 52 |
|-----------------|---|

End point description:

BMLs in 15 regions were measured with MRI, and graded as 0 (normal), 1 (mild; < 25% of region), 2 (moderate; 25% – 50% of region), or 3 (severe; > 50% of region). The global total BML score was the sum of the 15 component scores, and ranged from 0 (normal) to 45 (severe).

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 52 | |

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 56 | 66 | 61 | 66 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | 0.1 (-0.34 to 0.48) | 0.2 (-0.16 to 0.60) | 0.1 (-0.30 to 0.48) | 0.0 (-0.36 to 0.39) |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 122 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.602 ^[31] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.41 |
| upper limit | 0.7 |

Notes:

[31] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|----------------------------|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v ABT-981 100 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.953 ^[32] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.55 |
| upper limit | 0.58 |

Notes:

[32] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 122 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.83 ^[33] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.61 |
| upper limit | 0.49 |

Notes:

[33] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Secondary: Change from Baseline in Index Knee Intermittent and Constant Osteoarthritis Pain (ICOAP) Scores at Week 16

| | |
|-----------------|--|
| End point title | Change from Baseline in Index Knee Intermittent and Constant Osteoarthritis Pain (ICOAP) Scores at Week 16 |
|-----------------|--|

End point description:

The ICOAP is a multidimensional osteoarthritis-specific measure designed to comprehensively evaluate the pain experience in patients with hip or knee osteoarthritis. The ICOAP includes 11 items (5 constant pain items; 6 intermittent pain items). Each item is rated on a 0 to 4 point scale with a 7-day recall period. The raw maximum intermittent pain score ranges from 0 to 24, transformed to a reported scale of 0 (no pain) to 100 (worst pain). The raw maximum constant pain score ranges from 0 to 20, transformed to a reported scale of 0 (no pain) to 100 (worst pain).

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 16 | |

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|--------------------------|--------------------------|--------------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 75 | 84 | 76 | 77 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Intermittent pain | -20.2 (-24.32 to -16.08) | -19.5 (-23.40 to -15.58) | -21.3 (-25.40 to -17.26) | -18.8 (-22.92 to -14.71) |
| Constant pain | -18.6 (-22.88 to -14.33) | -17.7 (-21.73 to -13.62) | -24.2 (-28.39 to -19.94) | -20.0 (-24.24 to -15.72) |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|-------------------------|
| Statistical analysis description: | |
| Intermittent pain | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 159 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.804 ^[34] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.91 |
| upper limit | 6.33 |

Notes:

[34] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| Statistical analysis title | Statistical Analysis 2 |
|---|--------------------------|
| Statistical analysis description: | |
| Intermittent pain | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 151 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.699 ^[35] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.9 |
| upper limit | 4.63 |

Notes:

[35] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Intermittent pain

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.636 ^[36] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1.4 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.37 |
| upper limit | 7.14 |

Notes:

[36] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

Constant pain

| | |
|---|-------------------------|
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 159 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.756 ^[37] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.9 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.91 |
| upper limit | 6.76 |

Notes:

[37] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Constant pain

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 151 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.068 ^[38] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -5.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.55 |
| upper limit | 0.42 |

Notes:

[38] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Statistical analysis title

Statistical Analysis 6

Statistical analysis description:

Constant pain

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.649 ^[39] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.34 |
| upper limit | 4.58 |

Notes:

[39] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Secondary: Change from Baseline in ICOAP Scores at Week 26

| | |
|-----------------|---|
| End point title | Change from Baseline in ICOAP Scores at Week 26 |
|-----------------|---|

End point description:

The ICOAP is a multidimensional osteoarthritis-specific measure designed to comprehensively evaluate the pain experience in patients with hip or knee osteoarthritis. The ICOAP includes 11 items (5 constant pain items; 6 intermittent pain items). Each item is rated on a 0 to 4 point scale with a 7-day recall period. The raw maximum intermittent pain score ranges from 0 to 24, transformed to a reported scale of 0 (no pain) to 100 (worst pain). The raw maximum constant pain score ranges from 0 to 20, transformed to a reported scale of 0 (no pain) to 100 (worst pain).

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 26

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|--------------------------|--------------------------|--------------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 68 | 75 | 72 | 73 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Intermittent pain | -18.7 (-23.21 to -14.21) | -19.7 (-23.99 to -15.42) | -21.3 (-25.66 to -16.98) | -21.7 (-26.11 to -17.38) |
| Constant pain | -19.6 (-24.22 to -14.96) | -18.8 (-23.26 to -14.42) | -21.6 (-26.05 to -17.08) | -22.1 (-26.61 to -17.61) |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|-------------------------|
| Statistical analysis description: | |
| Intermittent pain | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 143 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.75 ^[40] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.14 |
| upper limit | 5.14 |

Notes:

[40] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| Statistical analysis title | Statistical Analysis 2 |
|---|--------------------------|
| Statistical analysis description: | |
| Intermittent pain | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 140 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.409 ^[41] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.6 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.82 |
| upper limit | 3.6 |

Notes:

[41] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Intermittent pain

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.338 ^[42] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -3 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.24 |
| upper limit | 3.18 |

Notes:

[42] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

Constant pain

| | |
|---|-------------------------|
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 143 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.817 ^[43] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.7 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.59 |
| upper limit | 7.08 |

Notes:

[43] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Constant pain

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 140 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.544 ^[44] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.37 |
| upper limit | 4.43 |

Notes:

[44] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Statistical analysis title

Statistical Analysis 6

Statistical analysis description:

Constant pain

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.437 ^[45] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.91 |
| upper limit | 3.86 |

Notes:

[45] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Secondary: Change from Baseline in ICOAP Scores at Week 52

| | |
|-----------------|---|
| End point title | Change from Baseline in ICOAP Scores at Week 52 |
|-----------------|---|

End point description:

The ICOAP is a multidimensional osteoarthritis-specific measure designed to comprehensively evaluate the pain experience in patients with hip or knee osteoarthritis. The ICOAP includes 11 items (5 constant pain items; 6 intermittent pain items). Each item is rated on a 0 to 4 point scale with a 7-day recall period. The raw maximum intermittent pain score ranges from 0 to 24, transformed to a reported scale of 0 (no pain) to 100 (worst pain). The raw maximum constant pain score ranges from 0 to 20, transformed to a reported scale of 0 (no pain) to 100 (worst pain).

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 52

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|--------------------------|--------------------------|--------------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 58 | 70 | 66 | 66 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Intermittent pain | -23.2 (-28.51 to -17.83) | -25.4 (-30.21 to -20.51) | -23.6 (-28.53 to -18.64) | -27.2 (-32.19 to -22.14) |
| Constant pain | -20.6 (-25.93 to -15.21) | -21.8 (-26.70 to -16.94) | -25.2 (-30.14 to -20.17) | -29.7 (-34.78 to -24.66) |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|--|-------------------------|
| Statistical analysis description: Intermittent pain | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 128 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.545 ^[46] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.31 |
| upper limit | 4.92 |

Notes:

[46] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| Statistical analysis title | Statistical Analysis 2 |
|--|--------------------------|
| Statistical analysis description: Intermittent pain | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.909 ^[47] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.65 |
| upper limit | 6.81 |

Notes:

[47] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Intermittent pain

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.278 ^[48] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -4 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.23 |
| upper limit | 3.25 |

Notes:

[48] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

Constant pain

| | |
|---|-------------------------|
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 128 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.732 ^[49] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.2 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.42 |
| upper limit | 5.92 |

Notes:

[49] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Constant pain

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.216 ^[50] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -4.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.86 |
| upper limit | 2.69 |

Notes:

[50] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

Constant pain

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.014 ^[51] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -9.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.42 |
| upper limit | -1.88 |

Notes:

[51] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Secondary: Change From Baseline In Index Knee Pain Intensity at Week 16

| | |
|-----------------|--|
| End point title | Change From Baseline In Index Knee Pain Intensity at Week 16 |
|-----------------|--|

End point description:

The index knee pain intensity was assessed in 3 different ways using an 11 -point NRS (0 to 10 points representing 'no pain' to 'worst possible pain'). Subjects were asked to enter: 1) average pain intensity during the past week (7-day recall period); 2) the worst pain during activity over the past 24 hours; 3) pain intensity before and after a 40 meter walk (performance pain, before and after). The 40 meter fast-paced walk test is a test of short distance walking activity, walking speed over short distances and changing direction during walking. Individuals taking the test should walk as quickly but as safely as possible, without running, along a walkway and then turn around, and repeat again for a total distance of 40 m (132 feet). The total time taken to walk the 40 meters is recorded.

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 16

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|-----------------------|-----------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 75 | 84 | 77 | 77 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| 7-Day Recall Period | -2.4 (-2.86 to -1.97) | -2.4 (-2.79 to -1.95) | -2.7 (-3.09 to -2.22) | -2.1 (-2.55 to -1.67) |
| Activity Pain | -2.3 (-2.85 to -1.82) | -2.4 (-2.85 to -1.87) | -2.7 (-3.19 to -2.17) | -2.1 (-2.59 to -1.56) |
| Performance Pain (Before) | -2.4 (-2.82 to -1.89) | -2.1 (-2.58 to -1.70) | -2.5 (-2.97 to -2.06) | -2.1 (-2.52 to -1.60) |
| Performance Pain (After) | -2.6 (-3.07 to -2.11) | -2.4 (-2.90 to -2.00) | -2.7 (-3.16 to -2.22) | -2.3 (-2.77 to -1.82) |

Statistical analyses

| | |
|--|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: 7-day recall period | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 159 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.874 ^[52] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.56 |
| upper limit | 0.66 |

Notes:

[52] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|--|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: 7-day recall period | |
| Comparison groups | Placebo v ABT-981 100 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.451 ^[53] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.86 |
| upper limit | 0.38 |

Notes:

[53] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: | |
| 7-day recall period | |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.331 ^[54] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.31 |
| upper limit | 0.93 |

Notes:

[54] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 4 |
| Statistical analysis description: | |
| Activity pain | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 159 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.932 ^[55] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.73 |
| upper limit | 0.67 |

Notes:

[55] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Activity pain

| | |
|---|--------------------------|
| Comparison groups | ABT-981 100 mg v Placebo |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.344 ^[56] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.07 |
| upper limit | 0.37 |

Notes:

[56] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

Activity pain

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.489 ^[57] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.3 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.47 |
| upper limit | 0.97 |

Notes:

[57] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 7 |
|-----------------------------------|------------------------|

| | |
|---|-------------------------|
| Statistical analysis description: | |
| Performance pain (before) | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 159 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.498 ^[58] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.42 |
| upper limit | 0.85 |

Notes:

[58] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 8 |
| Statistical analysis description: | |
| Performance pain (before) | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.637 ^[59] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 0.49 |

Notes:

[59] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 9 |
| Statistical analysis description: | |
| Performance pain (before) | |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.367 ^[60] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.35 |
| upper limit | 0.94 |

Notes:

[60] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 10 |
| Statistical analysis description: | |
| Performance pain (after) | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 159 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.67 ^[61] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.51 |
| upper limit | 0.79 |

Notes:

[61] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 11 |
| Statistical analysis description: | |
| Performance pain (after) | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.776 ^[62] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.76 |
| upper limit | 0.57 |

Notes:

[62] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 12 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Performance pain (after)

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.387 ^[63] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.37 |
| upper limit | 0.96 |

Notes:

[63] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Secondary: Change From Baseline In Index Knee Pain Intensity at Week 26

| | |
|-----------------|--|
| End point title | Change From Baseline In Index Knee Pain Intensity at Week 26 |
|-----------------|--|

End point description:

The index knee pain intensity was assessed in 3 different ways using an 11 -point NRS (0 to 10 points representing 'no pain' to 'worst possible pain'). Subjects were asked to enter: 1) average pain intensity during the past week (7-day recall period); 2) the worst pain during activity over the past 24 hours; 3) pain intensity before and after a 40 meter walk (performance pain, before and after). The 40 meter fast-paced walk test is a test of short distance walking activity, walking speed over short distances and changing direction during walking. Individuals taking the test should walk as quickly but as safely as possible, without running, along a walkway and then turn around, and repeat again for a total distance of 40 m (132 feet). The total time taken to walk the 40 meters is recorded.

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 26

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 68 ^[64] | 75 | 73 ^[65] | 73 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| 7-Day Recall Period | -2.2 (-2.76 to 1.73) | -2.4 (-2.89 to 1.91) | -2.8 (-3.29 to 2.31) | -2.5 (-2.98 to 1.99) |
| Activity Pain | -2.5 (-3.07 to 1.91) | -2.5 (-3.10 to 1.99) | -2.8 (-3.37 to 2.25) | -2.5 (-3.10 to 1.97) |
| Performance Pain (Before) | -2.2 (-2.72 to 1.70) | -2.2 (-2.68 to 1.71) | -2.6 (-3.13 to 2.16) | -2.7 (-3.15 to 2.17) |
| Performance Pain (After) | -2.5 (-3.01 to 1.98) | -2.4 (-2.90 to 1.92) | -3.0 (-3.53 to 2.54) | -2.6 (-3.13 to 2.13) |

Notes:

[64] - n=67 for Performance Pain (After)

[65] - n=72 for Performance Pain (After)

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|-------------------------|
| Statistical analysis description: | |
| 7-day recall period | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 143 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.661 ^[66] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.86 |
| upper limit | 0.54 |

Notes:

[66] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| Statistical analysis title | Statistical Analysis 2 |
|---|--------------------------|
| Statistical analysis description: | |
| 7-day recall period | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.122 ^[67] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.26 |
| upper limit | 0.15 |

Notes:

[67] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|
| Statistical analysis description: | |
| 7-day recall period | |

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.507 ^[68] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.94 |
| upper limit | 0.47 |

Notes:

[68] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 4 |
| Statistical analysis description: | |
| Activity pain | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 143 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.892 ^[69] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.85 |
| upper limit | 0.74 |

Notes:

[69] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 5 |
| Statistical analysis description: | |
| Activity pain | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.433 ^[70] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.12 |
| upper limit | 0.48 |

Notes:

[70] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

Activity pain

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.92 ^[71] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.84 |
| upper limit | 0.76 |

Notes:

[71] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

Performance pain (before)

| | |
|---|-------------------------|
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 143 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.957 ^[72] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.68 |
| upper limit | 0.71 |

Notes:

[72] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 8 |
|-----------------------------------|------------------------|

| | |
|---|--------------------------|
| Statistical analysis description: | |
| Performance pain (before) | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.222 ^[73] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.13 |
| upper limit | 0.26 |

Notes:

[73] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 9 |
| Statistical analysis description: | |
| Performance pain (before) | |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.209 ^[74] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.15 |
| upper limit | 0.25 |

Notes:

[74] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|--|-------------------------|
| Statistical analysis title | Statistical Analysis 10 |
| Statistical analysis description: | |
| Performance pain (after); n=67 for placebo group (subjects in this analysis =142, not the auto-calculated 143) | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 143 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.813 ^[75] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.62 |
| upper limit | 0.79 |

Notes:

[75] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 11 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Performance pain (after); n=67 for placebo group and n=72 for ABT-981 100 mg (subjects in this analysis =139, not the auto-calculated 141)

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.135 ^[76] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.25 |
| upper limit | 0.17 |

Notes:

[76] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 12 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Performance pain (after); n=67 for placebo group (subjects in this analysis =140, not the auto-calculated 141)

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.697 ^[77] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.85 |
| upper limit | 0.57 |

Notes:

[77] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Secondary: Change From Baseline In Index Knee Pain Intensity at Week 52

| | |
|--|--|
| End point title | Change From Baseline In Index Knee Pain Intensity at Week 52 |
| End point description: | |
| <p>The index knee pain intensity was assessed in 3 different ways using an 11 -point NRS (0 to 10 points representing 'no pain' to 'worst possible pain'). Subjects were asked to enter: 1) average pain intensity during the past week (7-day recall period); 2) the worst pain during activity over the past 24 hours; 3) pain intensity before and after a 40 meter walk (performance pain, before and after). The 40 meter fast-paced walk test is a test of short distance walking activity, walking speed over short distances and changing direction during walking. Individuals taking the test should walk as quickly but as safely as possible, without running, along a walkway and then turn around, and repeat again for a total distance of 40 m (132 feet). The total time taken to walk the 40 meters is recorded.</p> | |
| Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 52 | |

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 58 | 70 | 67 | 66 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| 7-Day Recall Period | -2.9 (-3.51 to 2.35) | -2.9 (-3.45 to 2.39) | -2.9 (-3.43 to 2.35) | -3.1 (-3.65 to 2.56) |
| Activity Pain | -2.8 (-3.48 to 2.16) | -3.0 (-3.64 to 2.43) | -3.2 (-3.77 to 2.55) | -3.0 (-3.65 to 2.40) |
| Performance Pain (Before) | -2.6 (-3.14 to 2.03) | -2.7 (-3.24 to 2.23) | -3.0 (-3.51 to 2.49) | -2.9 (-3.46 to 2.41) |
| Performance Pain (After) | -2.9 (-3.47 to 2.33) | -3.0 (-3.53 to 2.50) | -3.4 (-3.90 to 2.86) | -3.2 (-3.69 to 2.62) |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| 7-day recall period | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 128 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.978 ^[78] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.76 |
| upper limit | 0.79 |

Notes:

[78] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| 7-day recall period | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.925 ^[79] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.75 |
| upper limit | 0.82 |

Notes:

[79] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: | |
| 7-day recall period | |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.659 ^[80] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.96 |
| upper limit | 0.61 |

Notes:

[80] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 4 |
| Statistical analysis description: | |
| Activity pain | |
| Comparison groups | Placebo v ABT-981 25 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 128 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.633 ^[81] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 0.67 |

Notes:

[81] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 5 |
| Statistical analysis description: | |
| Activity pain | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.46 ^[82] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.23 |
| upper limit | 0.56 |

Notes:

[82] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 6 |
| Statistical analysis description: | |
| Activity pain | |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.663 ^[83] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 0.7 |

Notes:

[83] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 7 |
| Statistical analysis description: | |
| Performance pain (before) | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 128 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.696 ^[84] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.89 |
| upper limit | 0.59 |

Notes:

[84] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 8 |
| Statistical analysis description: | |
| Performance pain (before) | |
| Comparison groups | ABT-981 100 mg v Placebo |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.278 ^[85] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.16 |
| upper limit | 0.34 |

Notes:

[85] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 9 |
| Statistical analysis description: | |
| Performance pain (before) | |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.357 ^[86] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 0.4 |

Notes:

[86] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 10 |
| Statistical analysis description: | |
| Performance pain (after) | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 128 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.761 ^[87] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.87 |
| upper limit | 0.64 |

Notes:

[87] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|--------------------------|
| Statistical analysis title | Statistical Analysis 11 |
| Statistical analysis description: | |
| Performance pain (after) | |
| Comparison groups | Placebo v ABT-981 100 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.218 ^[88] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.25 |
| upper limit | 0.29 |

Notes:

[88] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 12 |
| Statistical analysis description: | |
| Performance pain (after) | |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.513 ^[89] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.02 |
| upper limit | 0.51 |

Notes:

[89] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Secondary: Change From Baseline in Patient Global Assessment (PGA) of Arthritis of the Index Knee at Week 16

| | |
|---|---|
| End point title | Change From Baseline in Patient Global Assessment (PGA) of Arthritis of the Index Knee at Week 16 |
| End point description: | |
| The PGA is a single item for evaluating overall osteoarthritis disease activity. PGA is assessed using an 11-point NRS of 0 to 10 points (representing best to worst disease status, respectively), with a 7-day recall period. | |
| Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 16 | |

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|-----------------------|-----------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 75 | 84 | 77 | 77 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -2.5 (-2.94 to -2.01) | -2.4 (-2.80 to -1.92) | -2.9 (-3.34 to -2.42) | -2.6 (-3.08 to -2.15) |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|-------------------------|
| Comparison groups | ABT-981 25 mg v Placebo |
| Number of subjects included in analysis | 159 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.728 ^[90] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.52 |
| upper limit | 0.75 |

Notes:

[90] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| Statistical analysis title | Statistical Analysis 2 |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.219 ^[91] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.06 |
| upper limit | 0.24 |

Notes:

[91] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.673 ^[92] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.79 |
| upper limit | 0.51 |

Notes:

[92] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each post-baseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Secondary: Change From Baseline in PGA of Arthritis of the Index Knee at Week 26

| | |
|-----------------|---|
| End point title | Change From Baseline in PGA of Arthritis of the Index Knee at Week 26 |
|-----------------|---|

End point description:

The PGA is a single item for evaluating overall osteoarthritis disease activity. PGA is assessed using an 11-point NRS of 0 to 10 points (representing best to worst disease status, respectively), with a 7-day recall period.

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 26 | |

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|-----------------------|-----------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 68 | 75 | 73 | 73 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -2.4 (-2.96 to -1.91) | -2.4 (-2.94 to -1.94) | -3.0 (-3.48 to -2.47) | -2.7 (-3.18 to -2.16) |

Statistical analyses

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v ABT-981 25 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 143 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.984 ^[93] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.73 |
| upper limit | 0.71 |

Notes:

[93] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.145 ^[94] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.26 |
| upper limit | 0.19 |

Notes:

[94] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.527 ^[95] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.96 |
| upper limit | 0.49 |

Notes:

[95] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Secondary: Change From Baseline in PGA of Arthritis of the Index Knee at Week 52

| | |
|-----------------|---|
| End point title | Change From Baseline in PGA of Arthritis of the Index Knee at Week 52 |
|-----------------|---|

End point description:

The PGA is a single item for evaluating overall osteoarthritis disease activity. PGA is assessed using an 11-point NRS of 0 to 10 points (representing best to worst disease status, respectively), with a 7-day recall period.

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 52

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|-----------------------|-----------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 58 | 70 | 67 | 66 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -3.0 (-3.62 to -2.44) | -2.9 (-3.48 to -2.41) | -3.2 (-3.71 to -2.62) | -3.5 (-4.01 to -2.89) |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 128 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.836 ^[96] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.71 |
| upper limit | 0.87 |

Notes:

[96] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|----------------------------|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v ABT-981 100 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.738 ^[97] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.94 |
| upper limit | 0.66 |

Notes:

[97] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3 ^[98] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.22 |
| upper limit | 0.38 |

Notes:

[98] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Secondary: Change From Baseline in Cartilage Volume of the Index Knee at Week 26

| | |
|-----------------|---|
| End point title | Change From Baseline in Cartilage Volume of the Index Knee at Week 26 |
|-----------------|---|

End point description:

Cartilage volume of the global knee, the medial central condyle + plateau, and the medial condyle + plateau was measured using MRI.

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 26 | |

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 58 | 65 | 53 | 66 |
| Units: mm ³ | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Global knee | -326.0 (-400.83 to -251.13) | -325.5 (-397.10 to -253.83) | -322.4 (-400.20 to -244.61) | -359.0 (-429.72 to -288.35) |
| Medial central condyle + plateau | -59.1 (-83.12 to -35.10) | -54.9 (-77.83 to -31.90) | -50.1 (-75.13 to -25.07) | -57.5 (-80.12 to -34.88) |
| Medial condyle + plateau | -128.6 (-166.76 to -90.50) | -126.5 (-163.03 to -90.02) | -124.5 (-164.13 to -84.86) | -114.9 (-150.86 to -78.90) |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|-------------------------|
| Statistical analysis description: | |
| Global knee | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 123 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.992 ^[99] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -101.59 |
| upper limit | 102.62 |

Notes:

[99] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| Statistical analysis title | Statistical Analysis 2 |
|---|--------------------------|
| Statistical analysis description: | |
| Global knee | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 111 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.948 ^[100] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 3.6 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -103.95 |
| upper limit | 111.1 |

Notes:

[100] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Global knee

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.523 ^[101] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -33.1 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -134.76 |
| upper limit | 68.65 |

Notes:

[101] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

Medial central condyle + plateau

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 123 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.799 ^[102] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 4.2 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -28.47 |
| upper limit | 36.95 |

Notes:

[102] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 5 |
|-----------------------------------|------------------------|

| | |
|---|--------------------------|
| Statistical analysis description: | |
| Medial central condyle + plateau | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 111 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.609 ^[103] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -25.62 |
| upper limit | 43.64 |

Notes:

[103] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 6 |
| Statistical analysis description: | |
| Medial central condyle + plateau | |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.923 ^[104] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -30.97 |
| upper limit | 34.19 |

Notes:

[104] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 7 |
| Statistical analysis description: | |
| Medial condyle + plateau | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 123 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.937 ^[105] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 2.1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -49.88 |
| upper limit | 54.08 |

Notes:

[105] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

Medial condyle + plateau

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 111 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.882 ^[106] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 4.1 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -50.68 |
| upper limit | 58.95 |

Notes:

[106] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 9 |
|-----------------------------------|------------------------|

Statistical analysis description:

Medial condyle + plateau

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.602 ^[107] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 13.8 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -38.05 |
| upper limit | 65.55 |

Notes:

[107] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Secondary: Change From Baseline in Cartilage Volume of the Index Knee at Week 52

| | |
|-----------------|---|
| End point title | Change From Baseline in Cartilage Volume of the Index Knee at |
|-----------------|---|

End point description:

Cartilage volume of the global knee, the medial central condyle + plateau, and the medial condyle + plateau was measured using MRI.

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases.

End point type Secondary

End point timeframe:

Baseline, Week 52

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 57 | 50 | 56 |
| Units: mm ³ | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Global knee | -557.0 (-659.86 to -454.10) | -598.7 (-694.66 to -502.76) | -554.3 (-654.92 to -453.60) | -583.1 (-678.88 to -487.23) |
| Medial central condyle + plateau | -101.2 (-134.56 to -67.79) | -126.3 (-157.5 to -95.09) | -90.1 (-122.89 to -57.29) | -113.0 (-144.08 to -81.84) |
| Medial condyle + plateau | -214.7 (-273.77 to -155.64) | -255.0 (-310.03 to -199.97) | -190.3 (-248.05 to -132.51) | -242.8 (-297.71 to -187.86) |

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| Global knee | |
| Comparison groups | ABT-981 25 mg v Placebo |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.554 ^[108] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -41.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -180.49 |
| upper limit | 97.04 |

Notes:

[108] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| Global knee | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.97 ^[109] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 2.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -140.86 |
| upper limit | 146.31 |

Notes:

[109] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: | |
| Global knee | |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.713 ^[110] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -26.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -165.47 |
| upper limit | 113.32 |

Notes:

[110] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 4 |
| Statistical analysis description: | |
| Medial central condyle + plateau | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.272 ^[111] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -25.1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -70.12 |
| upper limit | 19.88 |

Notes:

[111] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 5 |
| Statistical analysis description: Medial central condyle + plateau | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.64 ^[112] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 11.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -35.63 |
| upper limit | 57.8 |

Notes:

[112] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 6 |
| Statistical analysis description: Medial central condyle + plateau | |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.608 ^[113] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -11.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -56.94 |
| upper limit | 33.38 |

Notes:

[113] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 7 |
|-----------------------------------|------------------------|

| | |
|---|--------------------------|
| Statistical analysis description: | |
| Medial condyle + plateau | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.319 ^[114] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -40.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -119.88 |
| upper limit | 39.3 |

Notes:

[114] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 8 |
| Statistical analysis description: | |
| Medial condyle + plateau | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.56 ^[115] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 24.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -58.05 |
| upper limit | 106.91 |

Notes:

[115] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 9 |
| Statistical analysis description: | |
| Medial condyle + plateau | |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.489 ^[116] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -28.1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -107.97 |
| upper limit | 51.82 |

Notes:

[116] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Secondary: Change From Baseline in Cartilage Thickness of the Index Knee at Week 26

| | |
|-----------------|--|
| End point title | Change From Baseline in Cartilage Thickness of the Index Knee at Week 26 |
|-----------------|--|

End point description:

Cartilage thickness of the global knee, the medial central condyle + plateau, and the medial condyle + plateau was measured using MRI.

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 26

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|---------------------------|---------------------------|---------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 58 | 65 | 53 | 66 |
| Units: mm | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Global knee | -0.047 (-0.058 to -0.036) | -0.047 (-0.058 to -0.037) | -0.048 (-0.059 to -0.037) | -0.052 (-0.062 to -0.041) |
| Medial central condyle + plateau | -0.085 (-0.122 to -0.048) | -0.077 (-0.113 to -0.042) | -0.074 (-0.113 to -0.036) | -0.076 (-0.111 to -0.041) |
| Medial condyle + plateau | -0.046 (-0.060 to -0.031) | -0.045 (-0.059 to -0.031) | -0.047 (-0.062 to -0.032) | -0.044 (-0.058 to -0.031) |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Global knee

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 123 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.972 ^[117] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.015 |
| upper limit | 0.015 |

Notes:

[117] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Global knee

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 111 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.929 ^[118] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.001 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.017 |
| upper limit | 0.015 |

Notes:

[118] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Global knee

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.543 ^[119] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.005 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02 |
| upper limit | 0.01 |

Notes:

[119] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 4 |
|-----------------------------------|------------------------|

| | |
|---|--------------------------|
| Statistical analysis description: | |
| Medial central condyle + plateau | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 123 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.752 ^[120] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.008 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.043 |
| upper limit | 0.059 |

Notes:

[120] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 5 |
| Statistical analysis description: | |
| Medial central condyle + plateau | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 111 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.691 ^[121] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.011 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.042 |
| upper limit | 0.064 |

Notes:

[121] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 6 |
| Statistical analysis description: | |
| Medial central condyle + plateau | |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.71 ^[122] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.01 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.041 |
| upper limit | 0.06 |

Notes:

[122] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

Medial condyle + plateau

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 123 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.965 ^[123] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.019 |
| upper limit | 0.02 |

Notes:

[123] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

Medial condyle + plateau

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 111 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.885 ^[124] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.002 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.022 |
| upper limit | 0.019 |

Notes:

[124] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 9 |
|-----------------------------------|------------------------|

Statistical analysis description:

Medial condyle + plateau

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.887 ^[125] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.001 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.018 |
| upper limit | 0.021 |

Notes:

[125] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Secondary: Change From Baseline in Cartilage Thickness of the Index Knee at Week 52

| | |
|-----------------|--|
| End point title | Change From Baseline in Cartilage Thickness of the Index Knee at Week 52 |
|-----------------|--|

End point description:

Cartilage thickness of the global knee, the medial central condyle + plateau, and the medial condyle + plateau was measured using MRI.

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, observed cases.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 52 | |

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|--|---------------------------|---------------------------|---------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 57 | 50 | 56 |
| Units: mm | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Global knee | -0.081 (-0.095 to -0.066) | -0.085 (-0.099 to -0.072) | -0.081 (-0.095 to -0.067) | -0.083 (-0.097 to -0.070) |
| Medial central condyle + plateau | -0.136 (-0.187 to -0.084) | -0.176 (-0.224 to -0.127) | -0.113 (-0.163 to -0.062) | -0.141 (-0.190 to -0.093) |
| Medial condyle + plateau | -0.084 (-0.106 to -0.063) | -0.096 (-0.117 to -0.076) | -0.073 (-0.094 to -0.052) | -0.087 (-0.107 to -0.067) |

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| Global knee | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.619 ^[126] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.005 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.024 |
| upper limit | 0.014 |

Notes:

[126] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| Global knee | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.952 ^[127] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.001 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02 |
| upper limit | 0.019 |

Notes:

[127] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: | |
| Global knee | |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.765 ^[128] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.003 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.022 |
| upper limit | 0.016 |

Notes:

[128] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 4 |
| Statistical analysis description: Medial central condyle + plateau | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.258 ^[129] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.11 |
| upper limit | 0.03 |

Notes:

[129] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 5 |
| Statistical analysis description: Medial central condyle + plateau | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.535 ^[130] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.023 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.049 |
| upper limit | 0.094 |

Notes:

[130] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 6 |
|-----------------------------------|------------------------|

| | |
|---|--------------------------|
| Statistical analysis description: | |
| Medial central condyle + plateau | |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.866 ^[131] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.006 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.076 |
| upper limit | 0.064 |

Notes:

[131] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 7 |
| Statistical analysis description: | |
| Medial condyle + plateau | |
| Comparison groups | Placebo v ABT-981 25 mg |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.413 ^[132] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.012 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.041 |
| upper limit | 0.017 |

Notes:

[132] - P-value for test of difference between ABT-981 25 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 8 |
| Statistical analysis description: | |
| Medial condyle + plateau | |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.445 ^[133] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.012 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.018 |
| upper limit | 0.042 |

Notes:

[133] - P-value for test of difference between ABT-981 100 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 9 |
|-----------------------------------|------------------------|

Statistical analysis description:

Medial condyle + plateau

| | |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.835 ^[134] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.003 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.032 |
| upper limit | 0.026 |

Notes:

[134] - P-value for test of difference between ABT-981 200 mg dose group and Placebo at each postbaseline time point was from an ANCOVA model with treatment, age, and K-L grade as the main factors and baseline as a covariate.

Secondary: Outcome Measures in Rheumatology Clinical Trials/Osteoarthritis Research Society International (OMERACT/OARSI) Response Rate at Week 16

| | |
|-----------------|---|
| End point title | Outcome Measures in Rheumatology Clinical Trials/Osteoarthritis Research Society International (OMERACT/OARSI) Response Rate at Week 16 |
|-----------------|---|

End point description:

Percentage of subjects classified as OMERACT-OARSI responders at Week 16. A subject was considered an OMERACT-OARSI responder if any of the following 3 criteria were met: 1. WOMAC Pain (in 0 – 100 scale) improvement $\geq 50\%$ and absolute reduction ≥ 20 as compared to the baseline; or 2. WOMAC Function (in normalized 0 – 100 scale) improvement $\geq 50\%$ and absolute reduction ≥ 20 as compared to the baseline; or 3. At least 2 of the following 3 are met: WOMAC Pain improvement $\geq 20\%$ and absolute reduction (in normalized 0 – 100 scale) ≥ 10 as compared to the baseline; WOMAC Function improvement $\geq 20\%$ and absolute reduction (in normalized 0 – 100 scale) ≥ 10 as compared to the baseline; PGA improvement $\geq 20\%$ and absolute change (in normalized 0 – 100 scale) ≥ 10 as compared to the baseline. Response rate 95% confidence interval based on normal approximation.

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, LOCF.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 16

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|----------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 85 | 88 | 84 | 87 |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 60.0 (49.6 to 70.4) | 67.0 (57.2 to 76.9) | 72.6 (63.1 to 82.2) | 65.5 (55.5 to 75.5) |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|--------------------------|
| Comparison groups | ABT-981 25 mg v Placebo |
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.311 ^[135] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Response Rate Difference |
| Point estimate | 7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.3 |
| upper limit | 21.4 |

Notes:

[135] - P-value for test of difference between each ABT-981 dose group and Placebo was from a Cochran-Mantel-Haenszel test using age group and K-L grade as stratification factors.

| Statistical analysis title | Statistical Analysis 2 |
|---|--------------------------|
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.08 ^[136] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Response Rate Difference |
| Point estimate | 12.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.5 |
| upper limit | 26.7 |

Notes:

[136] - P-value for test of difference between each ABT-981 dose group and Placebo was from a Cochran-Mantel-Haenszel test using age group and K-L grade as stratification factors.

| Statistical analysis title | Statistical Analysis 3 |
|----------------------------|--------------------------|
| Comparison groups | ABT-981 200 mg v Placebo |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.435 ^[137] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Response Rate Difference |
| Point estimate | 5.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.9 |
| upper limit | 19.9 |

Notes:

[137] - P-value for test of difference between each ABT-981 dose group and Placebo was from a Cochran-Mantel-Haenszel test using age group and K-L grade as stratification factors.

Secondary: OMERACT/OARSI Response Rate at Week 26

| | |
|-----------------|--|
| End point title | OMERACT/OARSI Response Rate at Week 26 |
|-----------------|--|

End point description:

Percentage of subjects classified as OMERACT-OARSI responders at Week 26. A subject was considered an OMERACT-OARSI responder if any of the following 3 criteria were met: 1. WOMAC Pain (in 0 – 100 scale) improvement $\geq 50\%$ and absolute reduction ≥ 20 as compared to the baseline; or 2. WOMAC Function (in normalized 0 – 100 scale) improvement $\geq 50\%$ and absolute reduction ≥ 20 as compared to the baseline; or 3. At least 2 of the following 3 are met: WOMAC Pain improvement $\geq 20\%$ and absolute reduction (in normalized 0 – 100 scale) ≥ 10 as compared to the baseline; WOMAC Function improvement $\geq 20\%$ and absolute reduction (in normalized 0 – 100 scale) ≥ 10 as compared to the baseline; PGA improvement $\geq 20\%$ and absolute change (in normalized 0 – 100 scale) ≥ 10 as compared to the baseline. Response rate 95% confidence interval based on normal approximation.

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, LOCF.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 26

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|----------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 85 | 88 | 84 | 88 |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 62.4 (52.1 to 72.7) | 64.8 (54.8 to 74.8) | 66.7 (56.6 to 76.7) | 72.7 (63.4 to 82.0) |

Statistical analyses

| | |
|----------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v ABT-981 25 mg |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.744 ^[138] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Response Rate Difference |
| Point estimate | 2.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.9 |
| upper limit | 16.8 |

Notes:

[138] - P-value for test of difference between each ABT-981 dose group and Placebo was from a Cochran-Mantel-Haenszel test using age group and K-L grade as stratification factors.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.581 ^[139] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Response Rate Difference |
| Point estimate | 4.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.1 |
| upper limit | 18.7 |

Notes:

[139] - P-value for test of difference between each ABT-981 dose group and Placebo was from a Cochran-Mantel-Haenszel test using age group and K-L grade as stratification factors.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.146 ^[140] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Response Rate Difference |
| Point estimate | 10.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.5 |
| upper limit | 24.3 |

Notes:

[140] - P-value for test of difference between each ABT-981 dose group and Placebo was from a Cochran-Mantel-Haenszel test using age group and K-L grade as stratification factors.

Secondary: OMERACT/OARSI Response Rate at Week 52

| | |
|-----------------|--|
| End point title | OMERACT/OARSI Response Rate at Week 52 |
|-----------------|--|

End point description:

Percentage of subjects classified as OMERACT-OARSI responders at Week 52. A subject was considered an OMERACT-OARSI responder if any of the following 3 criteria were met: 1. WOMAC Pain (in 0 – 100 scale) improvement $\geq 50\%$ and absolute reduction ≥ 20 as compared to the baseline; or 2. WOMAC Function (in normalized 0 – 100 scale) improvement $\geq 50\%$ and absolute reduction ≥ 20 as compared to the baseline; or 3. At least 2 of the following 3 are met: WOMAC Pain improvement $\geq 20\%$ and absolute reduction (in normalized 0 – 100 scale) ≥ 10 as compared to the baseline; WOMAC Function improvement $\geq 20\%$ and absolute reduction (in normalized 0 – 100 scale) ≥ 10 as compared to the baseline; PGA improvement $\geq 20\%$ and absolute change (in normalized 0 – 100 scale) ≥ 10 as compared to the baseline. Response rate 95% confidence interval based on normal approximation.

Modified Intent to Treat population: all subjects who received at least 1 dose of study drug, LOCF.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 52

| End point values | Placebo | ABT-981 25 mg | ABT-981 100 mg | ABT-981 200 mg |
|----------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 85 | 88 | 84 | 88 |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 70.6 (60.9 to 80.3) | 69.3 (59.7 to 79.0) | 71.4 (61.8 to 81.1) | 72.7 (63.4 to 82.0) |

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | ABT-981 25 mg v Placebo |
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.824 ^[141] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Response Rate Difference |
| Point estimate | -1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.9 |
| upper limit | 12.4 |

Notes:

[141] - P-value for test of difference between each ABT-981 dose group and Placebo was from a Cochran-Mantel-Haenszel test using age group and K-L grade as stratification factors.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v ABT-981 100 mg |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.964 ^[142] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Response Rate Difference |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.8 |
| upper limit | 14.5 |

Notes:

[142] - P-value for test of difference between each ABT-981 dose group and Placebo was from a Cochran-Mantel-Haenszel test using age group and K-L grade as stratification factors.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v ABT-981 200 mg |
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.763 ^[143] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Response Rate Difference |
| Point estimate | 2.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.3 |
| upper limit | 15.6 |

Notes:

[143] - P-value for test of difference between each ABT-981 dose group and Placebo was from a Cochran-Mantel-Haenszel test using age group and K-L grade as stratification factors.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to Week 52 (or last dose of study drug) plus 70 days

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Matching placebo subcutaneously (SC) every 2 weeks (E2W)

| | |
|-----------------------|---------------|
| Reporting group title | ABT-981 25 mg |
|-----------------------|---------------|

Reporting group description:

25 mg ABT-981 SC E2W

| | |
|-----------------------|----------------|
| Reporting group title | ABT-981 100 mg |
|-----------------------|----------------|

Reporting group description:

100 mg ABT-981 SC E2W

| | |
|-----------------------|----------------|
| Reporting group title | ABT-981 200 mg |
|-----------------------|----------------|

Reporting group description:

200 mg ABT-981 SC E2W

| Serious adverse events | Placebo | ABT-981 25 mg | ABT-981 100 mg |
|---|--|------------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 85 (9.41%) | 11 / 89 (12.36%) | 8 / 85 (9.41%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| BASAL CELL CARCINOMA | Additional description: In addition to this one subject with an SAE of basal cell carcinoma, two other subjects developed basal cell carcinomas that were considered AEs but not SAEs, by the site investigator. | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 89 (1.12%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COLON ADENOMA | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 89 (1.12%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INVASIVE DUCTAL BREAST CARCINOMA | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LUNG CANCER METASTATIC | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| ANKLE FRACTURE | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 1 / 89 (1.12%) | 0 / 85 (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 |
| CERVICAL VERTEBRAL FRACTURE | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CONCUSSION | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 89 (1.12%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FALL | | | |
| subjects affected / exposed | 2 / 85 (2.35%) | 0 / 89 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HIP FRACTURE | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HUMERUS FRACTURE | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 89 (0.00%) | 0 / 85 (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 |
| JOINT INJURY | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LACERATION | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PROCEDURAL INTESTINAL PERFORATION | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 89 (1.12%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RADIUS FRACTURE | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 89 (0.00%) | 0 / 85 (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 |
| ROAD TRAFFIC ACCIDENT | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 89 (0.00%) | 0 / 85 (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 |
| SKULL FRACTURE | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 89 (0.00%) | 0 / 85 (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 |
| TIBIA FRACTURE | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 89 (0.00%) | 0 / 85 (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 |
| UPPER LIMB FRACTURE | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 89 (0.00%) | 0 / 85 (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 |
| Vascular disorders | | | |
| HYPERTENSION | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 89 (1.12%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| AQUEDUCTAL STENOSIS | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BRAIN OEDEMA | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CEREBRAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 89 (1.12%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYDROCEPHALUS | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PARKINSON'S DISEASE | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SEIZURE | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 89 (1.12%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SYNCOPE | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |

| | | | | |
|---|---|----------------|----------------|----------------|
| COLITIS | subjects affected / exposed | 0 / 85 (0.00%) | 1 / 89 (1.12%) | 0 / 85 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ENTERITIS | subjects affected / exposed | 0 / 85 (0.00%) | 1 / 89 (1.12%) | 0 / 85 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ENTEROCOLITIS | subjects affected / exposed | 1 / 85 (1.18%) | 0 / 89 (0.00%) | 0 / 85 (0.00%) |
| | occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PANCREATITIS | subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 0 / 85 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SMALL INTESTINAL OBSTRUCTION | subjects affected / exposed | 1 / 85 (1.18%) | 0 / 89 (0.00%) | 0 / 85 (0.00%) |
| | occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | | |
| CHOLECYSTITIS | subjects affected / exposed | 0 / 85 (0.00%) | 1 / 89 (1.12%) | 1 / 85 (1.18%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LIVER DISORDER | subjects affected / exposed | 1 / 85 (1.18%) | 0 / 89 (0.00%) | 0 / 85 (0.00%) |
| | occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | | |
| ALVEOLITIS ALLERGIC | subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 1 / 85 (1.18%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | | |
|---|---|----------------|----------------|----------------|
| ASTHMA | subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 1 / 85 (1.18%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DYSпноEA | subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 1 / 85 (1.18%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | | |
| NEPHROLITHIASIS | subjects affected / exposed | 0 / 85 (0.00%) | 1 / 89 (1.12%) | 0 / 85 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | | |
| ADRENAL HAEMORRHAGE | subjects affected / exposed | 0 / 85 (0.00%) | 1 / 89 (1.12%) | 0 / 85 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | | |
| BACK PAIN | subjects affected / exposed | 0 / 85 (0.00%) | 1 / 89 (1.12%) | 0 / 85 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OSTEOARTHRITIS | subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 1 / 85 (1.18%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | | |
| APPENDICITIS | subjects affected / exposed | 0 / 85 (0.00%) | 1 / 89 (1.12%) | 0 / 85 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DIVERTICULITIS | | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 89 (0.00%) | 0 / 85 (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 |
| PERITONITIS | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 89 (1.12%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMONIA | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 89 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 89 (0.00%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|--|--|--|
| Serious adverse events | ABT-981 200 mg | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 88 (4.55%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| BASAL CELL CARCINOMA | Additional description: In addition to this one subject with an SAE of basal cell carcinoma, two other subjects developed basal cell carcinomas that were considered AEs but not SAEs, by the site investigator. | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| COLON ADENOMA | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| INVASIVE DUCTAL BREAST CARCINOMA | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| LUNG CANCER METASTATIC | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| ANKLE FRACTURE | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CERVICAL VERTEBRAL FRACTURE | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CONCUSSION | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| FALL | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HIP FRACTURE | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HUMERUS FRACTURE | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| JOINT INJURY | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| LACERATION | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PROCEDURAL INTESTINAL PERFORATION | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RADIUS FRACTURE | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ROAD TRAFFIC ACCIDENT | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SKULL FRACTURE | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| TIBIA FRACTURE | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| UPPER LIMB FRACTURE | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| HYPERTENSION | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| AQUEDUCTAL STENOSIS | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BRAIN OEDEMA | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CEREBRAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYDROCEPHALUS | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PARKINSON'S DISEASE | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SEIZURE | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SYNCOPE | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |

| | | | |
|---|----------------|--|--|
| COLITIS | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ENTERITIS | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ENTEROCOLITIS | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PANCREATITIS | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SMALL INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| CHOLECYSTITIS | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| LIVER DISORDER | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| ALVEOLITIS ALLERGIC | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| ASTHMA | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DYSпноEA | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| NEPHROLITHIASIS | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| ADRENAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| BACK PAIN | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OSTEOARTHRITIS | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| APPENDICITIS | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DIVERTICULITIS | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PERITONITIS | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PNEUMONIA | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Placebo | ABT-981 25 mg | ABT-981 100 mg |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 66 / 85 (77.65%) | 63 / 89 (70.79%) | 65 / 85 (76.47%) |
| Investigations | | | |
| NEUTROPHIL COUNT DECREASED | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 3 / 89 (3.37%) | 13 / 85 (15.29%) |
| occurrences (all) | 2 | 12 | 53 |
| Injury, poisoning and procedural complications | | | |
| CONTUSION | | | |
| subjects affected / exposed | 3 / 85 (3.53%) | 9 / 89 (10.11%) | 2 / 85 (2.35%) |
| occurrences (all) | 3 | 9 | 2 |
| FALL | | | |
| subjects affected / exposed | 3 / 85 (3.53%) | 5 / 89 (5.62%) | 3 / 85 (3.53%) |
| occurrences (all) | 3 | 6 | 4 |
| LIGAMENT SPRAIN | | | |

| | | | |
|--|---|---|---|
| subjects affected / exposed occurrences (all) | 3 / 85 (3.53%) 3 | 6 / 89 (6.74%) 6 | 2 / 85 (2.35%) 2 |
| Vascular disorders HYPERTENSION subjects affected / exposed occurrences (all) | 6 / 85 (7.06%) 9 | 7 / 89 (7.87%) 8 | 5 / 85 (5.88%) 7 |
| Nervous system disorders DIZZINESS subjects affected / exposed occurrences (all) HEADACHE subjects affected / exposed occurrences (all) | 1 / 85 (1.18%) 1 22 / 85 (25.88%) 48 | 3 / 89 (3.37%) 3 14 / 89 (15.73%) 37 | 6 / 85 (7.06%) 8 14 / 85 (16.47%) 29 |
| Blood and lymphatic system disorders NEUTROPENIA subjects affected / exposed occurrences (all) | 1 / 85 (1.18%) 1 | 12 / 89 (13.48%) 22 | 12 / 85 (14.12%) 21 |
| General disorders and administration site conditions FATIGUE subjects affected / exposed occurrences (all) INJECTION SITE ERYTHEMA subjects affected / exposed occurrences (all) INJECTION SITE PAIN subjects affected / exposed occurrences (all) INJECTION SITE RASH subjects affected / exposed occurrences (all) INJECTION SITE REACTION subjects affected / exposed occurrences (all) PAIN subjects affected / exposed occurrences (all) | 12 / 85 (14.12%) 15 1 / 85 (1.18%) 1 7 / 85 (8.24%) 15 3 / 85 (3.53%) 28 0 / 85 (0.00%) 0 6 / 85 (7.06%) 8 | 4 / 89 (4.49%) 4 4 / 89 (4.49%) 11 2 / 89 (2.25%) 2 3 / 89 (3.37%) 26 6 / 89 (6.74%) 15 3 / 89 (3.37%) 3 | 5 / 85 (5.88%) 5 7 / 85 (8.24%) 36 2 / 85 (2.35%) 3 7 / 85 (8.24%) 24 8 / 85 (9.41%) 10 4 / 85 (4.71%) 7 |

| | | | |
|---|-----------------------------|------------------|------------------|
| Gastrointestinal disorders | | | |
| | DIARRHOEA | | |
| | subjects affected / exposed | 7 / 85 (8.24%) | 6 / 89 (6.74%) |
| | occurrences (all) | 9 | 7 |
| | | | |
| | NAUSEA | | |
| | subjects affected / exposed | 3 / 85 (3.53%) | 4 / 89 (4.49%) |
| | occurrences (all) | 3 | 7 |
| Respiratory, thoracic and mediastinal disorders | | | |
| | COUGH | | |
| | subjects affected / exposed | 5 / 85 (5.88%) | 7 / 89 (7.87%) |
| | occurrences (all) | 6 | 7 |
| | | | |
| | OROPHARYNGEAL PAIN | | |
| | subjects affected / exposed | 2 / 85 (2.35%) | 4 / 89 (4.49%) |
| | occurrences (all) | 2 | 7 |
| Skin and subcutaneous tissue disorders | | | |
| | PRURITUS | | |
| | subjects affected / exposed | 0 / 85 (0.00%) | 6 / 89 (6.74%) |
| | occurrences (all) | 0 | 7 |
| | | | |
| | RASH | | |
| | subjects affected / exposed | 3 / 85 (3.53%) | 2 / 89 (2.25%) |
| | occurrences (all) | 3 | 2 |
| Musculoskeletal and connective tissue disorders | | | |
| | ARTHRALGIA | | |
| | subjects affected / exposed | 16 / 85 (18.82%) | 16 / 89 (17.98%) |
| | occurrences (all) | 20 | 24 |
| | | | |
| | BACK PAIN | | |
| | subjects affected / exposed | 14 / 85 (16.47%) | 8 / 89 (8.99%) |
| | occurrences (all) | 15 | 9 |
| | | | |
| | MUSCULOSKELETAL PAIN | | |
| | subjects affected / exposed | 5 / 85 (5.88%) | 5 / 89 (5.62%) |
| | occurrences (all) | 7 | 6 |
| | | | |
| | MYALGIA | | |
| | subjects affected / exposed | 1 / 85 (1.18%) | 2 / 89 (2.25%) |
| | occurrences (all) | 1 | 2 |
| | | | |
| | PAIN IN EXTREMITY | | |

| | | | |
|--|------------------------|-----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 6 / 85 (7.06%) 8 | 5 / 89 (5.62%) 14 | 7 / 85 (8.24%) 7 |
| Infections and infestations | | | |
| BRONCHITIS | | | |
| subjects affected / exposed occurrences (all) | 2 / 85 (2.35%) 2 | 5 / 89 (5.62%) 6 | 1 / 85 (1.18%) 1 |
| INFLUENZA | | | |
| subjects affected / exposed occurrences (all) | 10 / 85 (11.76%) 17 | 2 / 89 (2.25%) 2 | 5 / 85 (5.88%) 5 |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed occurrences (all) | 16 / 85 (18.82%) 18 | 9 / 89 (10.11%) 10 | 13 / 85 (15.29%) 16 |
| SINUSITIS | | | |
| subjects affected / exposed occurrences (all) | 1 / 85 (1.18%) 1 | 5 / 89 (5.62%) 5 | 3 / 85 (3.53%) 5 |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed occurrences (all) | 8 / 85 (9.41%) 12 | 8 / 89 (8.99%) 8 | 7 / 85 (8.24%) 8 |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed occurrences (all) | 4 / 85 (4.71%) 5 | 3 / 89 (3.37%) 3 | 5 / 85 (5.88%) 5 |

| | | | |
|--|------------------------|--|--|
| Non-serious adverse events | ABT-981 200 mg | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 75 / 88 (85.23%) | | |
| Investigations | | | |
| NEUTROPHIL COUNT DECREASED | | | |
| subjects affected / exposed occurrences (all) | 13 / 88 (14.77%) 43 | | |
| Injury, poisoning and procedural complications | | | |
| CONTUSION | | | |
| subjects affected / exposed occurrences (all) | 5 / 88 (5.68%) 8 | | |
| FALL | | | |
| subjects affected / exposed occurrences (all) | 8 / 88 (9.09%) 9 | | |

| | | | |
|--|--|--|--|
| LIGAMENT SPRAIN subjects affected / exposed occurrences (all) | 2 / 88 (2.27%) 2 | | |
| Vascular disorders HYPERTENSION subjects affected / exposed occurrences (all) | 1 / 88 (1.14%) 1 | | |
| Nervous system disorders DIZZINESS subjects affected / exposed occurrences (all) HEADACHE subjects affected / exposed occurrences (all) | 3 / 88 (3.41%) 3 21 / 88 (23.86%) 34 | | |
| Blood and lymphatic system disorders NEUTROPENIA subjects affected / exposed occurrences (all) | 21 / 88 (23.86%) 41 | | |
| General disorders and administration site conditions FATIGUE subjects affected / exposed occurrences (all) INJECTION SITE ERYTHEMA subjects affected / exposed occurrences (all) INJECTION SITE PAIN subjects affected / exposed occurrences (all) INJECTION SITE RASH subjects affected / exposed occurrences (all) INJECTION SITE REACTION subjects affected / exposed occurrences (all) PAIN | 7 / 88 (7.95%) 8 5 / 88 (5.68%) 12 1 / 88 (1.14%) 1 8 / 88 (9.09%) 86 12 / 88 (13.64%) 30 | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 4 / 88 (4.55%) 4 | | |
| Gastrointestinal disorders | | | |
| DIARRHOEA | | | |
| subjects affected / exposed | 9 / 88 (10.23%) | | |
| occurrences (all) | 12 | | |
| NAUSEA | | | |
| subjects affected / exposed | 6 / 88 (6.82%) | | |
| occurrences (all) | 6 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| COUGH | | | |
| subjects affected / exposed | 5 / 88 (5.68%) | | |
| occurrences (all) | 5 | | |
| OROPHARYNGEAL PAIN | | | |
| subjects affected / exposed | 7 / 88 (7.95%) | | |
| occurrences (all) | 8 | | |
| Skin and subcutaneous tissue disorders | | | |
| PRURITUS | | | |
| subjects affected / exposed | 4 / 88 (4.55%) | | |
| occurrences (all) | 5 | | |
| RASH | | | |
| subjects affected / exposed | 4 / 88 (4.55%) | | |
| occurrences (all) | 4 | | |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 14 / 88 (15.91%) | | |
| occurrences (all) | 26 | | |
| BACK PAIN | | | |
| subjects affected / exposed | 14 / 88 (15.91%) | | |
| occurrences (all) | 17 | | |
| MUSCULOSKELETAL PAIN | | | |
| subjects affected / exposed | 4 / 88 (4.55%) | | |
| occurrences (all) | 4 | | |
| MYALGIA | | | |
| subjects affected / exposed | 9 / 88 (10.23%) | | |
| occurrences (all) | 11 | | |

| | | | |
|---|--|--|--|
| PAIN IN EXTREMITY subjects affected / exposed occurrences (all) | 5 / 88 (5.68%) 7 | | |
| Infections and infestations BRONCHITIS subjects affected / exposed occurrences (all) INFLUENZA subjects affected / exposed occurrences (all) NASOPHARYNGITIS subjects affected / exposed occurrences (all) SINUSITIS subjects affected / exposed occurrences (all) UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all) URINARY TRACT INFECTION subjects affected / exposed occurrences (all) | 4 / 88 (4.55%) 4 4 / 88 (4.55%) 5 17 / 88 (19.32%) 22 3 / 88 (3.41%) 3 12 / 88 (13.64%) 16 8 / 88 (9.09%) 9 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 08 October 2013 | Added secondary objective of safety and tolerability. |
| 28 January 2014 | Added additional questions to increase sensitivity of knee pain intensity measure and changed AE grading to CTCAE grading scale. |
| 01 April 2014 | Extended minimal post-dosing observational period to 1 hour, extended the assessment period of knee pain intensity prior to screening to 14 days to enhance selection of appropriate subjects, allowed for the use of low dose ibuprofen as an add-on rescue medication, and added subject discontinuation criteria due to lack of efficacy based on the subject's assessment of knee pain intensity scores. |
| 02 October 2014 | Expanded screening and washout periods to accommodate scheduling/assessment of screening imaging procedures, gave sites the option to use ultrasound or MRI imaging to detect synovitis during screening, clarified pregnancy testing requirements, included previous exposure to drugs of an immunosuppressive nature as exclusion criterion, allowed subjects with widened degree of moderate knee mal-alignment to be enrolled, further defined several abnormal laboratory values which were considered exclusionary, revised knee pain intensity to provide instructions for 40 meter fast-paced walk test, modified section for the collection and handling of PK and ADA samples, and added Appendix D to list various TB test scenarios. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported