



## Clinical trial results:

### A Phase 2a, Randomized, Double-blind, Placebo- and Naproxen-controlled, Parallel-group Study to Assess the Analgesic Efficacy of ASP7962 in Patients With Pain Due to Osteoarthritis of the Knee Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2014-004996-22    |
| Trial protocol           | BE HU GB CZ ES    |
| Global end of trial date | 29 September 2017 |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 20 June 2018 |
| First version publication date | 20 June 2018 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | 7962-CL-0022 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02611466 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Astellas Pharma Europe B.V.  |
| Sponsor organisation address | Sylviusweg 62, Leiden, Netherlands, 2333 BE  |
| Public contact               | Clinical Trial Disclosure, Astellas Pharma Europe B.V.,<br>Astellas.resultsdisclosure@astellas.com |
| Scientific contact           | Clinical Trial Disclosure, Astellas Pharma Europe B.V.,<br>Astellas.resultsdisclosure@astellas.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                       | 29 September 2017 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 29 September 2017 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study, conducted in participants with pain due to osteoarthritis (OA) of the knee, was to evaluate the analgesic efficacy of ASP7962 relative to placebo. The study consisted of a screening period (up to 3 weeks), a 1-week baseline period, a 4-week double-blind treatment period and a 4-week follow-up period.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 16 February 2016 |
| 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 | Belgium: 6         |
| Country: Number of subjects enrolled | Czech Republic: 20 |
| Country: Number of subjects enrolled | Germany: 64        |
| Country: Number of subjects enrolled | Hungary: 67        |
| Country: Number of subjects enrolled | Spain: 50          |
| Country: Number of subjects enrolled | United Kingdom: 8  |
| Worldwide total number of subjects   | 215                |
| EEA total number of subjects         | 215                |

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)                     | 108 |
| From 65 to 84 years                      | 107 |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Participants with pain due to OA of the knee were enrolled in sites in Western and Eastern Europe.

### Pre-assignment

Screening details:

Participants who met the screening criteria entered a washout of all pain medication for at least 7 days and recorded daily average pain ratings for at least 5 days in an e-diary. After entry criteria were reassessed, eligible participants were randomized to receive ASP7962, placebo or naproxen treatment in a ratio of 2:2:1.

### 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, Monitor, Subject, Data analyst |

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Participants received placebo orally twice daily for a period of 4 weeks.

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

Dosage and administration details:

Participants received matching placebo orally twice daily, in the morning and evening with or without food (approximately 12 hours).

|                  |         |
|------------------|---------|
| <b>Arm title</b> | ASP7962 |
|------------------|---------|

Arm description:

Participants received 100 mg of ASP7962 orally twice daily for 4 weeks.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | ASP7962      |
| Investigational medicinal product code | ASP7962      |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Participants received ASP7962 100 mg orally twice daily, in the morning and evening with or without food (approximately 12 hours).

|                  |          |
|------------------|----------|
| <b>Arm title</b> | Naproxen |
|------------------|----------|

Arm description:

Participants received 500 mg of Naproxen orally twice daily for 4 weeks.

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|  |          |
|--|----------|
| Investigational medicinal product name | Naproxen |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Participants received naproxen 500 mg orally twice daily, in the morning and evening with or without food (approximately 12 hours).

| <b>Number of subjects in period 1</b> | Placebo | ASP7962 | Naproxen |
|---------------------------------------|---------|---------|----------|
| Started                               | 87      | 85      | 43       |
| Completed                             | 77      | 79      | 40       |
| Not completed                         | 10      | 6       | 3        |
| Did Not Receive Study Drug            | 2       | -       | 1        |
| Adverse Event                         | 3       | 3       | 2        |
| Protocol Deviation                    | 2       | 2       | -        |
| Miscellaneous                         | -       | 1       | -        |
| Withdrawal by Subject                 | 3       | -       | -        |

## Baseline characteristics

### Reporting groups

|   |          |
|---|----------|
| Reporting group title   | Placebo  |
| Reporting group description:  |          |
| Participants received placebo orally twice daily for a period of 4 weeks. |          |
| Reporting group title   | ASP7962  |
| Reporting group description:  |          |
| Participants received 100 mg of ASP7962 orally twice daily for 4 weeks.   |          |
| Reporting group title   | Naproxen |
| Reporting group description:  |          |
| Participants received 500 mg of Naproxen orally twice daily for 4 weeks.  |          |

| Reporting group values | Placebo | ASP7962 | Naproxen |
|------------------------|---------|---------|----------|
| Number of subjects     | 87      | 85      | 43       |
| Age categorical        |         |         |          |
| Units: Subjects        |         |         |          |

|  |        |        |        |
|--|--------|--------|--------|
| Age continuous   |        |        |        |
| Units: years   |        |        |        |
| arithmetic mean  | 64.0   | 63.6   | 65.7   |
| standard deviation   | ± 8.4  | ± 8.4  | ± 7.5  |
| Gender categorical   |        |        |        |
| Units:   |        |        |        |
| Male   | 29     | 26     | 17     |
| Female   | 58     | 59     | 26     |
| Race   |        |        |        |
| Units: Subjects  |        |        |        |
| White  | 86     | 82     | 43     |
| Black or African American  | 1      | 1      | 0      |
| Asian  | 0      | 1      | 0      |
| Other  | 0      | 1      | 0      |
| Index Knee Location  |        |        |        |
| Units: Subjects  |        |        |        |
| Right  | 46     | 39     | 22     |
| Left   | 41     | 46     | 21     |
| Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain Subscale Score  |        |        |        |
| WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The pain subscale contains five questions that ask about pain during the last 48 hours caused by arthritis in the index knee. |        |        |        |
| Units: units on a scale  |        |        |        |
| arithmetic mean  | 5.63   | 6.08   | 5.83   |
| standard deviation   | ± 1.33 | ± 1.37 | ± 1.04 |
| WOMAC Stiffness Subscale Score   |        |        |        |
| WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or   |        |        |        |

|  |        |        |        |
|--|--------|--------|--------|
| hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The stiffness subscale contains two questions that ask about stiffness during the last 48 hours caused by the arthritis.   |        |        |        |
| Units: units on a scale  |        |        |        |
| arithmetic mean  | 5.78   | 6.20   | 5.88   |
| standard deviation   | ± 1.71 | ± 1.72 | ± 1.76 |
| WOMAC Physical Function Subscale Score   |        |        |        |
| WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The physical function subscale contains 17 questions that ask about the difficulty following daily physical activities.     |        |        |        |
| Units: units on a scale  |        |        |        |
| arithmetic mean  | 5.82   | 6.27   | 5.99   |
| standard deviation   | ± 1.37 | ± 1.40 | ± 0.99 |
| WOMAC Walking Pain Score   |        |        |        |
| WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The walking pain score is based on question 1 of the questionnaire on pain when walking on a flat surface.                  |        |        |        |
| Units: units on a scale  |        |        |        |
| arithmetic mean  | 5.54   | 6.12   | 6.02   |
| standard deviation   | ± 1.50 | ± 1.61 | ± 1.41 |
| WOMAC Total Score  |        |        |        |
| WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The total score is the sum of scores from pain, physical function and stiffness subscales. Total score ranges from 0 to 30. |        |        |        |
| Units: units on a scale  |        |        |        |
| arithmetic mean  | 17.22  | 18.54  | 17.71  |
| standard deviation   | ± 4.07 | ± 4.05 | ± 3.36 |
| Mean Daily Average Numerical Rating Scale (NRS) Pain Score: Index Knee   |        |        |        |
| The NRS is an 11-point scale used to capture the participant's average pain in the last 24 hours on a daily basis. This scale is composed of a single question and the score ranges from 0 to 10, where 0 anchors "no pain" and 10 anchors "pain as bad as you can imagine." The mean daily average NRS pain score was derived from the daily index knee pain ratings recorded by participants in an electronic diary (e-diary) on the last 4 days prior to randomization. Data only available for 214 participants [86, 85 43].   |        |        |        |
| Units: units on a scale  |        |        |        |
| arithmetic mean  | 6.15   | 6.26   | 6.40   |
| standard deviation   | ± 1.39 | ± 1.57 | ± 1.29 |
| Patient Global Assessment Score  |        |        |        |
| The PGA is an 11-point NRS scale used to capture the participant's overall impression at the time of the assessment in the index knee. This is a single question and the score ranges from 0 to 10, where 0 anchors "very good" and 10 anchors "very poor." Data only available for 211 participants [84, 84 43].  |        |        |        |
| Units: units on a scale  |        |        |        |
| arithmetic mean  | 5.98   | 6.36   | 6.23   |
| standard deviation   | ± 1.69 | ± 1.71 | ± 1.57 |
| <b>Reporting group values</b>  | Total  |        |        |
| Number of subjects   | 215    |        |        |

|  |     |  |  |
|--|-----|--|--|
| Age categorical<br>Units: Subjects   |     |  |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation  | -   |  |  |
| Gender categorical<br>Units:   |     |  |  |
| Male   | 72  |  |  |
| Female   | 143 |  |  |
| Race<br>Units: Subjects  |     |  |  |
| White  | 211 |  |  |
| Black or African American  | 2   |  |  |
| Asian  | 1   |  |  |
| Other  | 1   |  |  |
| Index Knee Location<br>Units: Subjects   |     |  |  |
| Right  | 107 |  |  |
| Left   | 108 |  |  |
| Western Ontario and McMaster<br>Universities Arthritis Index (WOMAC)<br>Pain Subscale Score  |     |  |  |
| WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The pain subscale contains five questions that ask about pain during the last 48 hours caused by arthritis in the index knee. |     |  |  |
| Units: units on a scale<br>arithmetic mean<br>standard deviation   | -   |  |  |
| WOMAC Stiffness Subscale Score   |     |  |  |
| WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The stiffness subscale contains two questions that ask about stiffness during the last 48 hours caused by the arthritis.      |     |  |  |
| Units: units on a scale<br>arithmetic mean<br>standard deviation   | -   |  |  |
| WOMAC Physical Function Subscale<br>Score  |     |  |  |
| WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The physical function subscale contains 17 questions that ask about the difficulty following daily physical activities.       |     |  |  |
| Units: units on a scale<br>arithmetic mean<br>standard deviation   | -   |  |  |
| WOMAC Walking Pain Score   |     |  |  |
| WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or   |     |  |  |



|  |   |  |  |
|--|---|--|--|
| hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The walking pain score is based on question 1 of the questionnaire on pain when walking on a flat surface.   |   |  |  |
| Units: units on a scale<br>arithmetic mean<br>standard deviation   | - |  |  |
| WOMAC Total Score  |   |  |  |
| WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The total score is the sum of scores from pain, physical function and stiffness subscales. Total score ranges from 0 to 30. |   |  |  |
| Units: units on a scale<br>arithmetic mean<br>standard deviation   | - |  |  |
| Mean Daily Average Numerical Rating Scale (NRS) Pain Score: Index Knee   |   |  |  |
| The NRS is an 11-point scale used to capture the participant's average pain in the last 24 hours on a daily basis. This scale is composed of a single question and the score ranges from 0 to 10, where 0 anchors "no pain" and 10 anchors "pain as bad as you can imagine." The mean daily average NRS pain score was derived from the daily index knee pain ratings recorded by participants in an electronic diary (e-diary) on the last 4 days prior to randomization. Data only available for 214 participants [86, 85 43].   |   |  |  |
| Units: units on a scale<br>arithmetic mean<br>standard deviation   | - |  |  |
| Patient Global Assessment Score  |   |  |  |
| The PGA is an 11-point NRS scale used to capture the participant's overall impression at the time of the assessment in the index knee. This is a single question and the score ranges from 0 to 10, where 0 anchors "very good" and 10 anchors "very poor." Data only available for 211 participants [84, 84 43].  |   |  |  |
| Units: units on a scale<br>arithmetic mean<br>standard deviation   | - |  |  |

## End points

### End points reporting groups

|   |          |
|---|----------|
| Reporting group title   | Placebo  |
| Reporting group description:  |          |
| Participants received placebo orally twice daily for a period of 4 weeks. |          |
| Reporting group title   | ASP7962  |
| Reporting group description:  |          |
| Participants received 100 mg of ASP7962 orally twice daily for 4 weeks.   |          |
| Reporting group title   | Naproxen |
| Reporting group description:  |          |
| Participants received 500 mg of Naproxen orally twice daily for 4 weeks.  |          |

### Primary: Change from Baseline to Week 4 in Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain Subscale Score

|   |   |
|---|---|
| End point title   | Change from Baseline to Week 4 in Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain Subscale Score |
| End point description:  |   |
| WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The pain subscale contains five questions that ask about pain during the last 48 hours caused by arthritis in the index knee. A negative change indicated a reduction/improvement from baseline. The analysis population was the full analysis set (FAS), which included all randomized participants who took at least 1 dose of study drug and who had a baseline and at least 1 double-blind treatment value for the WOMAC pain subscale score. Only participants with data available at baseline and at each timepoint were included. |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| Baseline and week 4   |   |

| End point values                    | Placebo         | ASP7962         | Naproxen        |  |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed         | 75              | 77              | 39              |  |
| Units: units on a scale             |                 |                 |                 |  |
| least squares mean (standard error) | -1.73 (± 0.21)  | -1.87 (± 0.20)  | -2.40 (± 0.28)  |  |

### Statistical analyses

|  |                                 |
|--|---------------------------------|
| Statistical analysis title   | Difference: ASP7962 vs. Placebo |
| Statistical analysis description:  |                                 |
| MMRM analysis was performed using change from baseline (week 1, 2 and 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline and week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean |                                 |

of placebo from the adjusted mean of treatment group.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 152                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.316 <sup>[1]</sup>                |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | Least Squares Mean (LSM) Difference   |
| Point estimate                          | -0.14                                 |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.62                                 |
| upper limit                             | 0.34                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.29                                  |

Notes:

[1] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo |
|-----------------------------------|----------------------------------|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 and 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline and week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v Naproxen                    |
| Number of subjects included in analysis | 114                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.027 <sup>[2]</sup>                |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.67                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.12                                 |
| upper limit                             | -0.23                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.35                                  |

Notes:

[2] - One-sided P-value for pairwise treatment comparison with placebo.

## **Secondary: Change from Baseline to End of Treatment (EOT) in WOMAC Pain Subscale Score**

|                 |   |
|-----------------|---|
| End point title | Change from Baseline to End of Treatment (EOT) in WOMAC Pain Subscale Score |
|-----------------|---|

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using

11-point NRS scale ranging from 0 (none) to 10 (extreme). The pain subscale contains five questions that ask about pain during the last 48 hours caused by arthritis in the index knee. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. The EOT value was defined as the last available postbaseline measurement within the treatment period.

|                                  |           |
|----------------------------------|-----------|
| End point type                   | Secondary |
| End point timeframe:             |           |
| Baseline and EOT (up to 4 weeks) |           |

| End point values                    | Placebo             | ASP7962             | Naproxen            |  |
|-------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                  | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed         | 79                  | 81                  | 42                  |  |
| Units: units on a scale             |                     |                     |                     |  |
| least squares mean (standard error) | -1.74 ( $\pm$ 0.20) | -1.91 ( $\pm$ 0.20) | -2.41 ( $\pm$ 0.27) |  |

## Statistical analyses

|   |                                 |
|---|---------------------------------|
| <b>Statistical analysis title</b>   | Difference: ASP7962 vs. Placebo |
| Statistical analysis description:   |                                 |
| Analysis of covariance (ANCOVA) model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. |                                 |
| Comparison groups   | Placebo v ASP7962               |
| Number of subjects included in analysis   | 160                             |
| Analysis specification  | Pre-specified                   |
| Analysis type   | superiority                     |
| P-value   | = 0.276 <sup>[3]</sup>          |
| Method  | ANCOVA                          |
| Parameter estimate  | LSM Difference                  |
| Point estimate  | -0.17                           |
| Confidence interval   |                                 |
| level   | 90 %                            |
| sides   | 2-sided                         |
| lower limit   | -0.63                           |
| upper limit   | 0.3                             |
| Variability estimate  | Standard error of the mean      |
| Dispersion value  | 0.28                            |

Notes:

[3] - One-sided P-value for pairwise treatment comparison with placebo.

|  |                                  |
|--|----------------------------------|
| <b>Statistical analysis title</b>  | Difference: Naproxen vs. Placebo |
| Statistical analysis description:  |                                  |
| ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. |                                  |
| Comparison groups  | Placebo v Naproxen               |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 121                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.025 <sup>[4]</sup>     |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSM Difference             |
| Point estimate                          | -0.66                      |
| Confidence interval                     |                            |
| level                                   | Other: 80 %                |
| sides                                   | 2-sided                    |
| lower limit                             | -1.1                       |
| upper limit                             | -0.23                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.34                       |

Notes:

[4] - One-sided P-value for pairwise treatment comparison with placebo.

## Secondary: Change from Baseline to EOT in WOMAC Physical Function Subscale Score

|                 |   |
|-----------------|---|
| End point title | Change from Baseline to EOT in WOMAC Physical Function Subscale Score |
|-----------------|---|

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The physical function subscale contains 17 questions that ask about the difficulty following daily physical activities. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. The EOT value was defined as the last available postbaseline measurement within the treatment period.

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

End point timeframe:

Baseline and EOT (up to 4 weeks)

| End point values                    | Placebo         | ASP7962         | Naproxen        |  |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed         | 79              | 81              | 42              |  |
| Units: units on a scale             |                 |                 |                 |  |
| least squares mean (standard error) | -1.67 (± 0.19)  | -1.81 (± 0.19)  | -2.51 (± 0.26)  |  |

## Statistical analyses

|                            |                                 |
|----------------------------|---------------------------------|
| Statistical analysis title | Difference: ASP7962 vs. Placebo |
|----------------------------|---------------------------------|

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

|                   |                   |
|-------------------|-------------------|
| Comparison groups | Placebo v ASP7962 |
|-------------------|-------------------|

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 160                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.306 <sup>[5]</sup>     |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSM Difference             |
| Point estimate                          | -0.14                      |
| Confidence interval                     |                            |
| level                                   | 90 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -0.59                      |
| upper limit                             | 0.31                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.27                       |

Notes:

[5] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo |
|-----------------------------------|----------------------------------|

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

|   |                            |
|---|----------------------------|
| Comparison groups                       | Placebo v Naproxen         |
| Number of subjects included in analysis | 121                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.005 <sup>[6]</sup>     |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSM Difference             |
| Point estimate                          | -0.84                      |
| Confidence interval                     |                            |
| level                                   | Other: 80 %                |
| sides                                   | 2-sided                    |
| lower limit                             | -1.26                      |
| upper limit                             | -0.42                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.33                       |

Notes:

[6] - One-sided P-value for pairwise treatment comparison with placebo.

## Secondary: Change from Baseline to EOT in WOMAC Stiffness Subscale Score

|                 |   |
|-----------------|---|
| End point title | Change from Baseline to EOT in WOMAC Stiffness Subscale Score |
|-----------------|---|

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The stiffness subscale contains two questions that ask about stiffness during the last 48 hours caused by the arthritis. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. The EOT value was defined as the last available postbaseline measurement within the treatment period.

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

End point timeframe:  
Baseline and EOT (up to 4 weeks)

| End point values                    | Placebo         | ASP7962         | Naproxen        |  |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed         | 79              | 81              | 42              |  |
| Units: units on a scale             |                 |                 |                 |  |
| least squares mean (standard error) | -1.68 (± 0.20)  | -1.89 (± 0.20)  | -2.82 (± 0.28)  |  |

## Statistical analyses

| Statistical analysis title | Difference ASP7962 vs. Placebo |
|----------------------------|--------------------------------|
|----------------------------|--------------------------------|

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

|   |                            |
|---|----------------------------|
| Comparison groups                       | Placebo v ASP7962          |
| Number of subjects included in analysis | 160                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.232 <sup>[7]</sup>     |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSM Difference             |
| Point estimate                          | -0.21                      |
| Confidence interval                     |                            |
| level                                   | 90 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -0.68                      |
| upper limit                             | 0.26                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.28                       |

Notes:

[7] - One-sided P-value for pairwise treatment comparison with placebo.

| Statistical analysis title | Difference: Naproxen vs. Placebo |
|----------------------------|----------------------------------|
|----------------------------|----------------------------------|

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

|   |                        |
|---|------------------------|
| Comparison groups                       | Placebo v Naproxen     |
| Number of subjects included in analysis | 121                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.001 <sup>[8]</sup> |
| Method                                  | ANCOVA                 |
| Parameter estimate                      | LSM Difference         |
| Point estimate                          | -1.14                  |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | Other: 80 %                |
| sides                | 2-sided                    |
| lower limit          | -1.58                      |
| upper limit          | -0.7                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.34                       |

Notes:

[8] - One-sided P-value for pairwise treatment comparison with placebo.

## Secondary: Change from Baseline to EOT in WOMAC Total Score

|                 |  |
|-----------------|--|
| End point title | Change from Baseline to EOT in WOMAC Total Score |
|-----------------|--|

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The total score is the sum of scores from pain, physical function and stiffness subscales. Total score ranges from 0 to 30. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. The EOT value was defined as the last available postbaseline measurement within the treatment period.

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

End point timeframe:

Baseline and EOT (up to 4 weeks)

| End point values                    | Placebo         | ASP7962         | Naproxen        |  |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed         | 79              | 81              | 42              |  |
| Units: units on a scale             |                 |                 |                 |  |
| least squares mean (standard error) | -5.07 (± 0.56)  | -5.65 (± 0.56)  | -7.71 (± 0.77)  |  |

## Statistical analyses

|                            |                                 |
|----------------------------|---------------------------------|
| Statistical analysis title | Difference: ASP7962 vs. Placebo |
|----------------------------|---------------------------------|

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

|   |                        |
|---|------------------------|
| Comparison groups                       | Placebo v ASP7962      |
| Number of subjects included in analysis | 160                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.232 <sup>[9]</sup> |
| Method                                  | ANCOVA                 |
| Parameter estimate                      | LSM Difference         |
| Point estimate                          | -0.59                  |



|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 90 %                       |
| sides                | 2-sided                    |
| lower limit          | -1.91                      |
| upper limit          | 0.74                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.8                        |

Notes:

[9] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo |
|-----------------------------------|----------------------------------|

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

|   |                            |
|---|----------------------------|
| Comparison groups                       | Placebo v Naproxen         |
| Number of subjects included in analysis | 121                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.003 <sup>[10]</sup>    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSM Difference             |
| Point estimate                          | -2.64                      |
| Confidence interval                     |                            |
| level                                   | Other: 80 %                |
| sides                                   | 2-sided                    |
| lower limit                             | -3.87                      |
| upper limit                             | -1.41                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.95                       |

Notes:

[10] - One-sided P-value for pairwise treatment comparison with placebo.

## Secondary: Change from Baseline to EOT in WOMAC Walking Pain Score

|                 |   |
|-----------------|---|
| End point title | Change from Baseline to EOT in WOMAC Walking Pain Score |
|-----------------|---|

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The walking pain score is based on question 1 of the questionnaire on pain when walking on a flat surface. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. The EOT value was defined as the last available postbaseline measurement within the treatment period.

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

End point timeframe:

Baseline and EOT (up to 4 weeks)

| End point values                    | Placebo         | ASP7962         | Naproxen        |  |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed         | 79              | 81              | 42              |  |
| Units: units on a scale             |                 |                 |                 |  |
| least squares mean (standard error) | -1.56 (± 0.22)  | -1.82 (± 0.21)  | -2.53 (± 0.29)  |  |

## Statistical analyses

| Statistical analysis title   | Difference: ASP7962 vs. Placebo |
|--|---------------------------------|
| Statistical analysis description:  |                                 |
| ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. |                                 |
| Comparison groups  | Placebo v ASP7962               |
| Number of subjects included in analysis  | 160                             |
| Analysis specification   | Pre-specified                   |
| Analysis type  | superiority                     |
| P-value  | = 0.197 <sup>[11]</sup>         |
| Method   | ANCOVA                          |
| Parameter estimate   | LSM Difference                  |
| Point estimate   | -0.26                           |
| Confidence interval  |                                 |
| level  | 90 %                            |
| sides  | 2-sided                         |
| lower limit  | -0.77                           |
| upper limit  | 0.24                            |
| Variability estimate   | Standard error of the mean      |
| Dispersion value   | 0.31                            |

Notes:

[11] - One-sided P-value for pairwise treatment comparison with placebo.

| Statistical analysis title   | Difference: Naproxen vs. Placebo |
|--|----------------------------------|
| Statistical analysis description:  |                                  |
| ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. |                                  |
| Comparison groups  | Placebo v Naproxen               |
| Number of subjects included in analysis  | 121                              |
| Analysis specification   | Pre-specified                    |
| Analysis type  | superiority                      |
| P-value  | = 0.005 <sup>[12]</sup>          |
| Method   | ANCOVA                           |
| Parameter estimate   | LSM Difference                   |
| Point estimate   | -0.96                            |
| Confidence interval  |                                  |
| level  | Other: 80 %                      |
| sides  | 2-sided                          |
| lower limit  | -1.44                            |
| upper limit  | -0.49                            |

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.37                       |

Notes:

[12] - One-sided P-value for pairwise treatment comparison with placebo.

## Secondary: Change from Baseline to Weeks 1 and 2 in WOMAC Pain Subscale Score

|                 |  |
|-----------------|--|
| End point title | Change from Baseline to Weeks 1 and 2 in WOMAC Pain Subscale Score |
|-----------------|--|

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The pain subscale contains five questions that ask about pain during the last 48 hours caused by arthritis in the index knee. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. N is the number of participants with data available at baseline and at each time point that were included in the analysis.

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

End point timeframe:

Baseline and Weeks 1 and 2

| End point values                    | Placebo         | ASP7962         | Naproxen        |  |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed         | 79              | 81              | 42              |  |
| Units: units on a scale             |                 |                 |                 |  |
| least squares mean (standard error) |                 |                 |                 |  |
| Week 1 [N=76, 79, 42]               | -1.13 (± 0.17)  | -1.12 (± 0.17)  | -1.90 (± 0.23)  |  |
| Week 2 [N=75, 80, 41]               | -1.19 (± 0.19)  | -1.49 (± 0.18)  | -1.83 (± 0.25)  |  |

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Difference: ASP7962 vs. Placebo (Week 1) |
|----------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.516 <sup>[13]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | 0.01                                  |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 90 %                       |
| sides                | 2-sided                    |
| lower limit          | -0.38                      |
| upper limit          | 0.4                        |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.24                       |

Notes:

[13] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 1) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v Naproxen                    |
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.003 <sup>[14]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.77                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.13                                 |
| upper limit                             | -0.41                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.28                                  |

Notes:

[14] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Difference: ASP7962 vs. Placebo (Week 2) |
|-----------------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.122 <sup>[15]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.31                                 |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 90 %                       |
| sides                | 2-sided                    |
| lower limit          | -0.74                      |
| upper limit          | 0.13                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.26                       |

Notes:

[15] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 2) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v Naproxen                    |
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.02 <sup>[16]</sup>                |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.64                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.05                                 |
| upper limit                             | -0.24                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.31                                  |

Notes:

[16] - One-sided P-value for pairwise treatment comparison with placebo.

### **Secondary: Change from Baseline to Weeks 1, 2 and 4 in WOMAC Physical Function Subscale Score**

|                 |  |
|-----------------|--|
| End point title | Change from Baseline to Weeks 1, 2 and 4 in WOMAC Physical Function Subscale Score |
|-----------------|--|

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The physical function subscale contains 17 questions that ask about the difficulty following daily physical activities. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. N is the number of participants with data available at baseline and at each time point that were included in the analysis.

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

End point timeframe:

Baseline and Weeks 1, 2, and 4

| End point values                    | Placebo         | ASP7962         | Naproxen        |  |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed         | 79              | 81              | 42              |  |
| Units: units on a scale             |                 |                 |                 |  |
| least squares mean (standard error) |                 |                 |                 |  |
| Week 1 [N=76, 79, 42]               | -1.00 (± 0.16)  | -1.07 (± 0.16)  | -1.87 (± 0.21)  |  |
| Week 2 [N=75, 80, 41]               | -1.14 (± 0.18)  | -1.42 (± 0.18)  | -1.92 (± 0.24)  |  |
| Week 4 [N=75, 77, 39]               | -1.65 (± 0.20)  | -1.77 (± 0.20)  | -2.48 (± 0.27)  |  |

## Statistical analyses

| Statistical analysis title  | Difference: ASP7962 vs. Placebo (Week 1) |
|---|--|
| Statistical analysis description:   |  |
| MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit. |  |
| Comparison groups   | Placebo v ASP7962                        |
| Number of subjects included in analysis   | 160                                      |
| Analysis specification  | Pre-specified                            |
| Analysis type   | superiority                              |
| P-value   | = 0.375 <sup>[17]</sup>                  |
| Method  | Mixed-effect model, Repeated measures    |
| Parameter estimate  | LSM Difference                           |
| Point estimate  | -0.07                                    |
| Confidence interval   |  |
| level   | 90 %                                     |
| sides   | 2-sided                                  |
| lower limit   | -0.44                                    |
| upper limit   | 0.3                                      |
| Variability estimate  | Standard error of the mean               |
| Dispersion value  | 0.22                                     |

Notes:

[17] - One-sided P-value for pairwise treatment comparison with placebo.

| Statistical analysis title  | Difference: Naproxen vs. Placebo (Week 1) |
|---|---|
| Statistical analysis description:   |   |
| MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit. |   |
| Comparison groups   | Placebo v Naproxen                        |

|   |                                       |
|---|---------------------------------------|
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | < 0.001 <sup>[18]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.88                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.21                                 |
| upper limit                             | -0.54                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.26                                  |

Notes:

[18] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Difference: ASP7962 vs. Placebo (Week 2) |
|-----------------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.132 <sup>[19]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.28                                 |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.69                                 |
| upper limit                             | 0.13                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.25                                  |

Notes:

[19] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 2) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|                   |                    |
|-------------------|--------------------|
| Comparison groups | Placebo v Naproxen |
|-------------------|--------------------|

|   |                                       |
|---|---------------------------------------|
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | equivalence                           |
| P-value                                 | = 0.005 <sup>[20]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.77                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.16                                 |
| upper limit                             | -0.39                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.3                                   |

Notes:

[20] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Difference: ASP7962 vs. Placebo (Week 4) |
|-----------------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.335 <sup>[21]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.12                                 |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.58                                 |
| upper limit                             | 0.34                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.28                                  |

Notes:

[21] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 4) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|                   |                    |
|-------------------|--------------------|
| Comparison groups | Placebo v Naproxen |
|-------------------|--------------------|



|   |                                       |
|---|---------------------------------------|
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.007 <sup>[22]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.83                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.26                                 |
| upper limit                             | -0.4                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.33                                  |

Notes:

[22] - One-sided P-value for pairwise treatment comparison with placebo.

## Secondary: Change from Baseline to Weeks 1, 2 and 4 in WOMAC Stiffness Subscale Score

|                 |  |
|-----------------|--|
| End point title | Change from Baseline to Weeks 1, 2 and 4 in WOMAC Stiffness Subscale Score |
|-----------------|--|

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The stiffness subscale contains two questions that ask about stiffness during the last 48 hours caused by the arthritis. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. N is the number of participants with data available at baseline and at each time point that were included in the analysis.

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

End point timeframe:

Baseline and Weeks 1, 2, and 4

| End point values                    | Placebo         | ASP7962         | Naproxen        |  |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed         | 79              | 81              | 42              |  |
| Units: units on a scale             |                 |                 |                 |  |
| least squares mean (standard error) |                 |                 |                 |  |
| Week 1 [N=76, 79, 42]               | -1.20 (± 0.18)  | -1.24 (± 0.18)  | -2.11 (± 0.25)  |  |
| Week 2 [N=75, 80, 41]               | -1.32 (± 0.19)  | -1.52 (± 0.19)  | -2.39 (± 0.26)  |  |
| Week 4 [N=75, 77, 39]               | -1.66 (± 0.20)  | -1.83 (± 0.20)  | -2.81 (± 0.28)  |  |

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Difference: ASP7962 vs. Placebo (Week 1) |
|----------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment

group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.439 <sup>[23]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.04                                 |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.46                                 |
| upper limit                             | 0.38                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.25                                  |

Notes:

[23] - One-sided P-value for pairwise treatment comparison with placebo..

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 1) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v Naproxen                    |
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.002 <sup>[24]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.9                                  |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.3                                  |
| upper limit                             | -0.51                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.3                                   |

Notes:

[24] - One-sided P-value for pairwise treatment comparison with placebo..

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Difference: ASP7962 vs. Placebo (Week 2) |
|-----------------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo

from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.217 <sup>[25]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.21                                 |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.65                                 |
| upper limit                             | 0.23                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.27                                  |

Notes:

[25] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 2) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v Naproxen                    |
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | < 0.001 <sup>[26]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -1.08                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.49                                 |
| upper limit                             | -0.67                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.32                                  |

Notes:

[26] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Difference: ASP7962 vs. Placebo (Week 4) |
|-----------------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|                   |                   |
|-------------------|-------------------|
| Comparison groups | Placebo v ASP7962 |
|-------------------|-------------------|

|   |                                       |
|---|---------------------------------------|
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.278 <sup>[27]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.17                                 |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.64                                 |
| upper limit                             | 0.3                                   |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.28                                  |

Notes:

[27] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 4) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v Naproxen                    |
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | < 0.001 <sup>[28]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -1.16                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.6                                  |
| upper limit                             | -0.71                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.34                                  |

Notes:

[28] - One-sided P-value for pairwise treatment comparison with placebo.

## Secondary: Change from Baseline to Weeks 1, 2 and 4 in WOMAC Total Score

|                 |   |
|-----------------|---|
| End point title | Change from Baseline to Weeks 1, 2 and 4 in WOMAC Total Score |
|-----------------|---|

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The total score is the sum of scores from pain, physical function and stiffness subscales. Total score ranges from 0 to 30. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. N is the number of participants with data available at baseline and at each time point that were included in the analysis.

|                                |           |
|--------------------------------|-----------|
| End point type                 | Secondary |
| End point timeframe:           |           |
| Baseline and Weeks 1, 2, and 4 |           |

| End point values                    | Placebo         | ASP7962         | Naproxen        |  |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed         | 79              | 81              | 42              |  |
| Units: units on a scale             |                 |                 |                 |  |
| least squares mean (standard error) |                 |                 |                 |  |
| Week 1 [N=76, 79, 42]               | -3.30 (± 0.48)  | -3.50 (± 0.47)  | -5.84 (± 0.64)  |  |
| Week 2 [N=75, 80, 41]               | -3.63 (± 0.52)  | -4.50 (± 0.52)  | -6.11 (± 0.71)  |  |
| Week 4 [N=75, 77, 39]               | -5.02 (± 0.58)  | -5.54 (± 0.57)  | -7.66 (± 0.79)  |  |

## Statistical analyses

| Statistical analysis title | Difference: ASP7962 vs. Placebo (Week 1) |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.379 <sup>[29]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.2                                  |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -1.3                                  |
| upper limit                             | 0.89                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.66                                  |

Notes:

[29] - One-sided P-value for pairwise treatment comparison with placebo.

| Statistical analysis title | Difference: Naproxen vs. Placebo (Week 1) |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|                   |                    |
|-------------------|--------------------|
| Comparison groups | Placebo v Naproxen |
|-------------------|--------------------|

|   |                                       |
|---|---------------------------------------|
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | < 0.001 <sup>[30]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -2.54                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -3.56                                 |
| upper limit                             | -1.53                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.79                                  |

Notes:

[30] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Difference: ASP7962 vs. Placebo (Week 2) |
|-----------------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.117 <sup>[31]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.88                                 |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -2.09                                 |
| upper limit                             | 0.34                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.73                                  |

Notes:

[31] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 2) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|                   |                    |
|-------------------|--------------------|
| Comparison groups | Placebo v Naproxen |
|-------------------|--------------------|

|   |                                       |
|---|---------------------------------------|
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.003 <sup>[32]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -2.48                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -3.61                                 |
| upper limit                             | -1.36                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.87                                  |

Notes:

[32] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Difference: ASP7962 vs. Placebo (Week 4) |
|-----------------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.261 <sup>[33]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.52                                 |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -1.86                                 |
| upper limit                             | 0.82                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.81                                  |

Notes:

[33] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 4) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|                   |                    |
|-------------------|--------------------|
| Comparison groups | Placebo v Naproxen |
|-------------------|--------------------|

|   |                                       |
|---|---------------------------------------|
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.004 <sup>[34]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -2.64                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -3.89                                 |
| upper limit                             | -1.39                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.97                                  |

Notes:

[34] - One-sided P-value for pairwise treatment comparison with placebo.

## Secondary: Change from Baseline to Weeks 1, 2 and 4 in WOMAC Walking Pain Score

|  |  |
|--|--|
| End point title  | Change from Baseline to Weeks 1, 2 and 4 in WOMAC Walking Pain Score |
| End point description:   |  |
| WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The walking pain score is based on question 1 of the questionnaire on pain when walking on a flat surface. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. N is the number of participants with data available at baseline and at each time point that were included in the analysis. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Baseline and Weeks 1, 2, and 4   |  |

| End point values                    | Placebo         | ASP7962         | Naproxen        |  |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed         | 79              | 81              | 42              |  |
| Units: units on a scale             |                 |                 |                 |  |
| least squares mean (standard error) |                 |                 |                 |  |
| Week 1 [N=76, 79, 42]               | -0.91 (± 0.20)  | -0.90 (± 0.19)  | -1.80 (± 0.26)  |  |
| Week 2 [N=75, 80, 41]               | -0.95 (± 0.21)  | -1.33 (± 0.21)  | -1.92 (± 0.28)  |  |
| Week 4 [N=75, 77, 39]               | -1.56 (± 0.23)  | -1.78 (± 0.22)  | -2.52 (± 0.31)  |  |

## Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | Difference: ASP7962 vs. Placebo (Week 1) |
| Statistical analysis description:  |  |
| MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment |  |



group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.518 <sup>[35]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | 0.01                                  |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.44                                 |
| upper limit                             | 0.46                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.27                                  |

Notes:

[35] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 1) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v Naproxen                    |
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.003 <sup>[36]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.89                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.31                                 |
| upper limit                             | -0.48                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.32                                  |

Notes:

[36] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Difference: ASP7962 vs. Placebo (Week 2) |
|-----------------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo

from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | equivalence                           |
| P-value                                 | = 0.101 <sup>[37]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.38                                 |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.86                                 |
| upper limit                             | 0.11                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.29                                  |

Notes:

[37] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 2) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v Naproxen                    |
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.003 <sup>[38]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.97                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.42                                 |
| upper limit                             | -0.52                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.35                                  |

Notes:

[38] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Difference: ASP7962 vs. Placebo (Week 4) |
|-----------------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|                   |                   |
|-------------------|-------------------|
| Comparison groups | Placebo v ASP7962 |
|-------------------|-------------------|

|   |                                       |
|---|---------------------------------------|
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.243 <sup>[39]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.22                                 |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.74                                 |
| upper limit                             | 0.3                                   |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.32                                  |

Notes:

[39] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 4) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v Naproxen                    |
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.006 <sup>[40]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.96                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.45                                 |
| upper limit                             | -0.47                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.38                                  |

Notes:

[40] - One-sided P-value for pairwise treatment comparison with placebo.

## Secondary: Change from Baseline to Weeks 1, 2, 3, 4 and EOT in Mean Daily Average Pain Score Assessed by the Numerical Rating Scale

|                 |  |
|-----------------|--|
| End point title | Change from Baseline to Weeks 1, 2, 3, 4 and EOT in Mean Daily Average Pain Score Assessed by the Numerical Rating Scale |
|-----------------|--|

End point description:

The NRS is an 11-point scale used to capture the participant's average pain in the last 24 hours on a daily basis. This scale is composed of a single question and the score ranges from 0 to 10, where 0 anchors "no pain" and 10 anchors "pain as bad as you can imagine." The mean daily average NRS pain score was derived from the daily index knee pain ratings recorded by participants in an electronic diary (e-diary) on the last 4 days prior to randomization. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. N is the number of

participants with data available at baseline and at each time point that were included in the analysis. The EOT value was defined as the last available postbaseline measurement within the treatment period.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:                                  |           |
| Baseline and Weeks 1, 2, 3, 4 and EOT (up to 4 weeks) |           |

| End point values                    | Placebo         | ASP7962         | Naproxen        |  |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed         | 79              | 81              | 42              |  |
| Units: units on a scale             |                 |                 |                 |  |
| least squares mean (standard error) |                 |                 |                 |  |
| Week 1 [N=78, 81, 42]               | -0.61 (± 0.15)  | -0.58 (± 0.15)  | -1.38 (± 0.21)  |  |
| Week 2 [N=77, 81, 42]               | -1.17 (± 0.17)  | -0.96 (± 0.17)  | -1.96 (± 0.23)  |  |
| Week 3 [N=77, 80, 41]               | -1.40 (± 0.19)  | -1.20 (± 0.19)  | -2.22 (± 0.26)  |  |
| Week 4 [N=77, 80, 40]               | -1.59 (± 0.20)  | -1.42 (± 0.19)  | -2.26 (± 0.27)  |  |
| EOT [N=78, 81, 42]                  | -1.60 (± 0.19)  | -1.49 (± 0.19)  | -2.30 (± 0.26)  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Difference: ASP7962 vs. Placebo (Week 1) |
| Statistical analysis description:   |  |
| MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit. |  |
| Comparison groups   | Placebo v ASP7962                        |
| Number of subjects included in analysis   | 160                                      |
| Analysis specification  | Pre-specified                            |
| Analysis type   | superiority                              |
| P-value   | = 0.555 <sup>[41]</sup>                  |
| Method  | Mixed-effect model, Repeated measures    |
| Parameter estimate  | LSM Difference                           |
| Point estimate  | 0.03                                     |
| Confidence interval   |  |
| level   | 90 %                                     |
| sides   | 2-sided                                  |
| lower limit   | -0.32                                    |
| upper limit   | 0.38                                     |
| Variability estimate  | Standard error of the mean               |
| Dispersion value  | 0.21                                     |

Notes:

[41] - One-sided P-value for pairwise treatment comparison with placebo.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Difference: Naproxen vs. Placebo (Week 1) |
| Statistical analysis description:  |   |
| MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment |   |

group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v Naproxen                    |
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.001 <sup>[42]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.77                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.1                                  |
| upper limit                             | -0.44                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.25                                  |

Notes:

[42] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Difference: ASP7962 vs. Placebo (Week 2) |
|-----------------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.807 <sup>[43]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | 0.21                                  |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.19                                 |
| upper limit                             | 0.6                                   |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.24                                  |

Notes:

[43] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 2) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo

from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v Naproxen                    |
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.003 <sup>[44]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.79                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.16                                 |
| upper limit                             | -0.42                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.29                                  |

Notes:

[44] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Difference: ASP7962 vs. Placebo (Week 3) |
|-----------------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.775 <sup>[45]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | 0.2                                   |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.24                                 |
| upper limit                             | 0.64                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.26                                  |

Notes:

[45] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 3) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|                   |                    |
|-------------------|--------------------|
| Comparison groups | Placebo v Naproxen |
|-------------------|--------------------|

|   |                                       |
|---|---------------------------------------|
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.005 <sup>[46]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.83                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.24                                 |
| upper limit                             | -0.42                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.32                                  |

Notes:

[46] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Difference: ASP7962 vs. Placebo (Week 4) |
|-----------------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.734 <sup>[47]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | 0.17                                  |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.28                                 |
| upper limit                             | 0.63                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.28                                  |

Notes:

[47] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 4) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|                   |                    |
|-------------------|--------------------|
| Comparison groups | Placebo v Naproxen |
|-------------------|--------------------|

|   |                                       |
|---|---------------------------------------|
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.023 <sup>[48]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.67                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.1                                  |
| upper limit                             | -0.24                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.33                                  |

Notes:

[48] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |                                       |
|-----------------------------------|---------------------------------------|
| <b>Statistical analysis title</b> | Difference: ASP7962 vs. Placebo (EOT) |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number analyzed is calculated incorrectly due to system limitation.

|   |                            |
|---|----------------------------|
| Comparison groups                       | Placebo v ASP7962          |
| Number of subjects included in analysis | 160                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.653 <sup>[49]</sup>    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSM Difference             |
| Point estimate                          | 0.11                       |
| Confidence interval                     |                            |
| level                                   | 90 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -0.34                      |
| upper limit                             | 0.55                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.27                       |

Notes:

[49] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (EOT) |
|-----------------------------------|--|

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number analyzed is calculated incorrectly due to system limitation.

|                   |                    |
|-------------------|--------------------|
| Comparison groups | Placebo v Naproxen |
|-------------------|--------------------|



|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 121                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.016 <sup>[50]</sup>    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSM Difference             |
| Point estimate                          | -0.71                      |
| Confidence interval                     |                            |
| level                                   | Other: 80 %                |
| sides                                   | 2-sided                    |
| lower limit                             | -1.13                      |
| upper limit                             | -0.29                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.33                       |

Notes:

[50] - One-sided P-value for pairwise treatment comparison with placebo.

## Secondary: Change from Baseline Patient Global Assessment (PGA) at Weeks 1, 2, 4 and EOT

|                 |   |
|-----------------|---|
| End point title | Change from Baseline Patient Global Assessment (PGA) at Weeks 1, 2, 4 and EOT |
|-----------------|---|

End point description:

The PGA is an 11-point NRS scale used to capture the participant's overall impression at the time of the assessment in the index knee. This is a single question and the score ranges from 0 to 10, where 0 anchors "very good" and 10 anchors "very poor." A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. N is the number of participants with data available at baseline and at each time point that were included in the analysis. The EOT value was defined as the last available postbaseline measurement within the treatment period.

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

End point timeframe:

Baseline and Weeks 1, 2, 4 and EOT (up to 4 weeks)

| End point values                    | Placebo         | ASP7962         | Naproxen        |  |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed         | 79              | 81              | 42              |  |
| Units: units on a scale             |                 |                 |                 |  |
| least squares mean (standard error) |                 |                 |                 |  |
| Week 1 [N=75, 79, 42]               | -1.15 (± 0.20)  | -1.27 (± 0.19)  | -1.71 (± 0.26)  |  |
| Week 2 [N=74, 80, 41]               | -1.25 (± 0.21)  | -1.55 (± 0.20)  | -2.02 (± 0.28)  |  |
| Week 4 [N=73, 77, 39]               | -1.57 (± 0.24)  | -1.97 (± 0.23)  | -2.43 (± 0.32)  |  |
| EOT [N=78, 81, 42]                  | -1.56 (± 0.23)  | -1.99 (± 0.22)  | -2.48 (± 0.31)  |  |

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Difference: ASP7962 vs. Placebo (Week 1) |
|----------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline

interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.324 <sup>[51]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.13                                 |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.58                                 |
| upper limit                             | 0.33                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.27                                  |

Notes:

[51] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 1) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v Naproxen                    |
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.042 <sup>[52]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.57                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -0.98                                 |
| upper limit                             | -0.15                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.33                                  |

Notes:

[52] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Difference: ASP7962 vs. Placebo (Week 2) |
|-----------------------------------|--|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v ASP7962                     |
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.148 <sup>[53]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.3                                  |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.78                                 |
| upper limit                             | 0.17                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.29                                  |

Notes:

[53] - One-sided P-value for pairwise treatment comparison with placebo.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Difference: Naproxen vs. Placebo (Week 2) |
| Statistical analysis description:   |   |
| MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit. |   |
| Comparison groups   | Placebo v Naproxen                        |
| Number of subjects included in analysis   | 121                                       |
| Analysis specification  | Pre-specified                             |
| Analysis type   | superiority                               |
| P-value   | = 0.013 <sup>[54]</sup>                   |
| Method  | Mixed-effect model, Repeated measures     |
| Parameter estimate  | LSM Difference                            |
| Point estimate  | -0.77                                     |
| Confidence interval   |   |
| level   | Other: 80 %                               |
| sides   | 2-sided                                   |
| lower limit   | -1.22                                     |
| upper limit   | -0.33                                     |
| Variability estimate  | Standard error of the mean                |
| Dispersion value  | 0.35                                      |

Notes:

[54] - One-sided P-value for pairwise treatment comparison with placebo.

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Difference: ASP7962 vs. Placebo (Week 4) |
| Statistical analysis description:   |  |
| MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit. |  |
| Comparison groups   | Placebo v ASP7962                        |

|   |                                       |
|---|---------------------------------------|
| Number of subjects included in analysis | 160                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.112 <sup>[55]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.4                                  |
| Confidence interval                     |                                       |
| level                                   | 90 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.95                                 |
| upper limit                             | 0.14                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.33                                  |

Notes:

[55] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (Week 4) |
|-----------------------------------|---|

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | Placebo v Naproxen                    |
| Number of subjects included in analysis | 121                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.015 <sup>[56]</sup>               |
| Method                                  | Mixed-effect model, Repeated measures |
| Parameter estimate                      | LSM Difference                        |
| Point estimate                          | -0.87                                 |
| Confidence interval                     |                                       |
| level                                   | Other: 80 %                           |
| sides                                   | 2-sided                               |
| lower limit                             | -1.38                                 |
| upper limit                             | -0.36                                 |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 0.4                                   |

Notes:

[56] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |                                       |
|-----------------------------------|---------------------------------------|
| <b>Statistical analysis title</b> | Difference: ASP7962 vs. Placebo (EOT) |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number analyzed is calculated incorrectly due to system limitation.

|                   |                   |
|-------------------|-------------------|
| Comparison groups | Placebo v ASP7962 |
|-------------------|-------------------|

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 160                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.088 <sup>[57]</sup>    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSM Difference             |
| Point estimate                          | -0.44                      |
| Confidence interval                     |                            |
| level                                   | 90 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -0.97                      |
| upper limit                             | 0.1                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.32                       |

Notes:

[57] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo (EOT) |
|-----------------------------------|--|

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number analyzed is calculated incorrectly due to system limitation.

|   |                            |
|---|----------------------------|
| Comparison groups                       | Placebo v Naproxen         |
| Number of subjects included in analysis | 121                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.009 <sup>[58]</sup>    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSM Difference             |
| Point estimate                          | -0.92                      |
| Confidence interval                     |                            |
| level                                   | Other: 80 %                |
| sides                                   | 2-sided                    |
| lower limit                             | -1.42                      |
| upper limit                             | -0.42                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.39                       |

Notes:

[58] - One-sided P-value for pairwise treatment comparison with placebo.

## Secondary: Percentage of Participants who Achieved $\geq 30\%$ Decrease from Baseline to EOT in WOMAC Pain Subscale Score

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants who Achieved $\geq 30\%$ Decrease from Baseline to EOT in WOMAC Pain Subscale Score |
|-----------------|--|

End point description:

Percentage of participants who had a reduction from baseline to EOT in WOMAC pain subscale score of  $\geq 30\%$  is reported. WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The pain subscale contains five questions that ask about pain during the last 48 hours caused by arthritis in the index knee. The analysis population was the FAS. Only participants with data at baseline or EOT were included

in the analysis. The EOT value was defined as the last available postbaseline measurement within the treatment period.

|                                  |           |
|----------------------------------|-----------|
| End point type                   | Secondary |
| End point timeframe:             |           |
| Baseline and EOT (up to 4 weeks) |           |

| End point values                  | Placebo           | ASP7962             | Naproxen            |  |
|-----------------------------------|-------------------|---------------------|---------------------|--|
| Subject group type                | Reporting group   | Reporting group     | Reporting group     |  |
| Number of subjects analysed       | 79                | 81                  | 42                  |  |
| Units: percentage of participants |                   |                     |                     |  |
| number (confidence interval 90%)  | 43 (33.6 to 52.9) | 53.1 (43.4 to 62.6) | 64.3 (50.5 to 76.5) |  |

## Statistical analyses

|                                   |                                 |
|-----------------------------------|---------------------------------|
| <b>Statistical analysis title</b> | Difference: ASP7962 vs. Placebo |
|-----------------------------------|---------------------------------|

Statistical analysis description:

Differences of the percentages were calculated by subtracting the percentage of placebo group from the percentage of the active treatment group. Confidence interval for each treatment group and the difference of the percentage was an exact unconditional confidence interval based on Santner-Snell approach.

|   |                         |
|---|-------------------------|
| Comparison groups                       | Placebo v ASP7962       |
| Number of subjects included in analysis | 160                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.133 <sup>[59]</sup> |
| Method                                  | Fisher exact            |
| Parameter estimate                      | Percentage Difference   |
| Point estimate                          | 10                      |
| Confidence interval                     |                         |
| level                                   | 90 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | -3.2                    |
| upper limit                             | 23.2                    |

Notes:

[59] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo |
|-----------------------------------|----------------------------------|

Statistical analysis description:

Differences of the percentages were calculated by subtracting the percentage of placebo group from the percentage of the active treatment group. Confidence interval for each treatment group and the difference of the percentage was an exact unconditional confidence interval based on Santner-Snell approach.

|                   |                    |
|-------------------|--------------------|
| Comparison groups | Placebo v Naproxen |
|-------------------|--------------------|

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 121                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.021 <sup>[60]</sup> |
| Method                                  | Fisher exact            |
| Parameter estimate                      | Percentage Difference   |
| Point estimate                          | 21.2                    |
| Confidence interval                     |                         |
| level                                   | Other: 80 %             |
| sides                                   | 2-sided                 |
| lower limit                             | 8.8                     |
| upper limit                             | 33.1                    |

Notes:

[60] - One-sided P-value for pairwise treatment comparison with placebo.

## Secondary: Percentage of Participants who Achieved $\geq 50\%$ Decrease from Baseline to EOT in WOMAC Pain Subscale Score

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants who Achieved $\geq 50\%$ Decrease from Baseline to EOT in WOMAC Pain Subscale Score |
|-----------------|--|

End point description:

Percentage of participants who had a reduction from baseline to EOT in WOMAC pain subscale score of  $\geq 50\%$  is reported. WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The pain subscale contains five questions that ask about pain during the last 48 hours caused by arthritis in the index knee. The analysis population was the FAS. Only participants with data at baseline or EOT were included in the analysis. The EOT value was defined as the last available postbaseline measurement within the treatment period.

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

End point timeframe:

Baseline and EOT (up to 4 weeks)

| End point values                  | Placebo             | ASP7962             | Naproxen            |  |
|-----------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed       | 79                  | 81                  | 42                  |  |
| Units: percentage of participants |                     |                     |                     |  |
| number (confidence interval 90%)  | 22.8 (15.3 to 31.9) | 32.1 (23.6 to 41.7) | 45.2 (32.0 to 59.0) |  |

## Statistical analyses

|                            |                                 |
|----------------------------|---------------------------------|
| Statistical analysis title | Difference: ASP7962 vs. Placebo |
|----------------------------|---------------------------------|

Statistical analysis description:

Differences of the percentages were calculated by subtracting the percentage of placebo group from the percentage of the active treatment group. Confidence interval for each treatment group and the difference of the percentage was an exact unconditional confidence interval based on Santner-Snell approach.

|                   |                   |
|-------------------|-------------------|
| Comparison groups | Placebo v ASP7962 |
|-------------------|-------------------|

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 160                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.127 <sup>[61]</sup> |
| Method                                  | Fisher exact            |
| Parameter estimate                      | Percentage Difference   |
| Point estimate                          | 9.3                     |
| Confidence interval                     |                         |
| level                                   | 90 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | -3.7                    |
| upper limit                             | 22.2                    |

Notes:

[61] - One-sided P-value for pairwise treatment comparison with placebo.

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | Difference: Naproxen vs. Placebo |
|-----------------------------------|----------------------------------|

Statistical analysis description:

Differences of the percentages were calculated by subtracting the percentage of placebo group from the percentage of the active treatment group. Confidence interval for each treatment group and the difference of the percentage was an exact unconditional confidence interval based on Santner-Snell approach.

|   |                        |
|---|------------------------|
| Comparison groups                       | Placebo v Naproxen     |
| Number of subjects included in analysis | 121                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.01 <sup>[62]</sup> |
| Method                                  | Fisher exact           |
| Parameter estimate                      | Percentage Difference  |
| Point estimate                          | 22.5                   |
| Confidence interval                     |                        |
| level                                   | Other: 80 %            |
| sides                                   | 2-sided                |
| lower limit                             | 10.1                   |
| upper limit                             | 34.3                   |

Notes:

[62] - One-sided P-value for pairwise treatment comparison with placebo.

## Secondary: Number of Participants with Treatment-Emergent Adverse Events

|                 |   |
|-----------------|---|
| End point title | Number of Participants with Treatment-Emergent Adverse Events |
|-----------------|---|

End point description:

A TEAE was defined as an adverse event (AE) which started or worsened after the first dose of study drug until 30 days after taking the last dose of study drug. This included abnormal laboratory tests, vital signs or electrocardiogram data that were defined as AEs if the abnormality induced clinical signs or symptoms, required active intervention, interruption or discontinuation of study drug or was clinically significant in the investigator's opinion. The analysis population was the safety analysis set (SAF), which consisted of all randomized participants who took at least 1 dose of double-blind study drug.

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

End point timeframe:

From first dose of study drug up to 30 days after last dose of study drug (up to 8 weeks)



| <b>End point values</b>                           | Placebo         | ASP7962         | Naproxen        |  |
|---|-----------------|-----------------|-----------------|--|
| Subject group type                                | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed                       | 85              | 85              | 42              |  |
| Units: participants                               |                 |                 |                 |  |
| TEAE  | 24              | 31              | 13              |  |
| Drug-related TEAE                                 | 10              | 8               | 7               |  |
| Serious TEAE                                      | 0               | 1               | 0               |  |
| Drug-related serious TEAE                         | 0               | 0               | 0               |  |
| Deaths  | 0               | 0               | 0               |  |
| TEAE leading to withdrawal of treatment           | 3               | 3               | 2               |  |
| Drug-related TEAE leading to treatment withdrawal | 3               | 1               | 2               |  |
| Joint-related TEAE                                | 1               | 3               | 2               |  |
| Neurological-related TEAE                         | 2               | 4               | 0               |  |
| Hepatic-related TEAE                              | 0               | 0               | 1               |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with an Affirmative Response in Columbia – Suicide Severity Rating Scale (C-SSRS): Suicidal Ideation

|                 |   |
|-----------------|---|
| End point title | Number of Participants with an Affirmative Response in Columbia – Suicide Severity Rating Scale (C-SSRS): Suicidal Ideation |
|-----------------|---|

End point description:

C-SSRS is a questionnaire used for suicide assessment. The data presented are the number of participants with an affirmative ("YES") response to questions: (1) Wish to be dead; (2) Non-specific active suicidal thoughts; (3) Active suicidal ideation with any methods (not plan) without intent to act; (4) Active suicidal ideation with some intent to act, without specific plan; and (5) Active suicidal ideation with specific plan and intent. The participant's worst finding in the treatment period or follow-up period is reported. The analysis population was the SAF. N is the number of participants with data available at each time point.

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

End point timeframe:

From first dose of study drug up to end of study (up to 8 weeks)

| <b>End point values</b>         | Placebo         | ASP7962         | Naproxen        |  |
|---------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type              | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed     | 85              | 85              | 42              |  |
| Units: participants             |                 |                 |                 |  |
| Treatment period [N=79, 82, 42] | 0               | 0               | 0               |  |
| Follow-up period [N=77, 81, 42] | 0               | 1               | 0               |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with an Affirmative Response in C-SSRS: Suicidal Behavior

|                 |  |
|-----------------|--|
| End point title | Number of Participants with an Affirmative Response in C-SSRS: Suicidal Behavior |
|-----------------|--|

End point description:

C-SSRS is a questionnaire used for suicide assessment. The data presented are the number of participants with an affirmative ("YES") response to questions: (1) Preparatory acts or behavior; (2) Aborted attempt; (3) Interrupted attempt; (4) Actual attempt; and (5) Completed suicide. The participant's worst finding in the treatment period or follow-up period is reported. The analysis population was the SAF. N is the number of participants with data available at each time point.

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

End point timeframe:

From first dose of study drug up to end of study (up to 8 weeks)

| End point values                | Placebo         | ASP7962         | Naproxen        |  |
|---------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type              | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed     | 85              | 85              | 42              |  |
| Units: participants             |                 |                 |                 |  |
| Treatment period [N=79, 82, 42] | 0               | 0               | 0               |  |
| Follow-up period [N=77, 81, 42] | 0               | 0               | 0               |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with an Affirmative Response in C-SSRS: Suicidal Ideation or Behavior

|                 |  |
|-----------------|--|
| End point title | Number of Participants with an Affirmative Response in C-SSRS: Suicidal Ideation or Behavior |
|-----------------|--|

End point description:

C-SSRS is a questionnaire used for suicide assessment. The data presented are the number of participants with an affirmative ("YES") response to any one of the ten suicidal ideation and behavior questions. The participant's worst finding in the treatment period or follow-up period is reported. The analysis population was the SAF. N is the number of participants with data available at each time point.

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

End point timeframe:

From first dose of study drug up to end of study (up to 8 weeks)

| End point values                | Placebo         | ASP7962         | Naproxen        |  |
|---------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type              | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed     | 85              | 85              | 42              |  |
| Units: participants             |                 |                 |                 |  |
| Treatment period [N=79, 82, 42] | 0               | 0               | 0               |  |
| Follow-up period [N=77, 81, 42] | 0               | 1               | 0               |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with an Affirmative Response in C-SSRS: Self-injurious Behavior without Suicidal Intent

|                 |  |
|-----------------|--|
| End point title | Number of Participants with an Affirmative Response in C-SSRS: Self-injurious Behavior without Suicidal Intent |
|-----------------|--|

End point description:

C-SSRS is a questionnaire used for suicide assessment. The data presented are the number of participants with an affirmative ("YES") response to the question "Has subject engaged in Non-Suicidal Self-Injurious Behavior?" The participant's worst finding in the treatment period or follow-up period is reported. The analysis population was the SAF. N is the number of participants with data available at each time point.

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

End point timeframe:

From first dose of study drug up to end of study (up to 8 weeks)

| End point values                | Placebo         | ASP7962         | Naproxen        |  |
|---------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type              | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed     | 85              | 85              | 42              |  |
| Units: participants             |                 |                 |                 |  |
| Treatment period [N=79, 82, 42] | 0               | 1               | 0               |  |
| Follow-up period [N=77, 81, 42] | 0               | 1               | 0               |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 30 days after last dose of study drug (up to 8 weeks)

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Participants received placebo orally twice daily for a period of 4 weeks.

|                       |         |
|-----------------------|---------|
| Reporting group title | ASP7962 |
|-----------------------|---------|

Reporting group description:

Participants received 100 mg of ASP7962 orally twice daily for 4 weeks.

|                       |          |
|-----------------------|----------|
| Reporting group title | Naproxen |
|-----------------------|----------|

Reporting group description:

Participants received 500 mg of Naproxen orally twice daily for 4 weeks.

| Serious adverse events                            | Placebo        | ASP7962        | Naproxen       |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events |                |                |                |
| subjects affected / exposed                       | 0 / 85 (0.00%) | 1 / 85 (1.18%) | 0 / 42 (0.00%) |
| number of deaths (all causes)                     | 0              | 0              | 0              |
| number of deaths resulting from adverse events    |                |                |                |
| Musculoskeletal and connective tissue disorders   |                |                |                |
| Arthralgia  |                |                |                |
| subjects affected / exposed                       | 0 / 85 (0.00%) | 1 / 85 (1.18%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |

Frequency threshold for reporting non-serious adverse events: 4 %

| Non-serious adverse events                            | Placebo        | ASP7962        | Naproxen        |
|---|----------------|----------------|-----------------|
| Total subjects affected by non-serious adverse events |                |                |                 |
| subjects affected / exposed                           | 8 / 85 (9.41%) | 8 / 85 (9.41%) | 5 / 42 (11.90%) |
| Ear and labyrinth disorders                           |                |                |                 |
| Vertigo   |                |                |                 |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 4 / 85 (4.71%)<br>9 | 4 / 85 (4.71%)<br>4 | 0 / 42 (0.00%)<br>0 |
| Gastrointestinal disorders                       |                     |                     |                     |
| Abdominal discomfort                             |                     |                     |                     |
| subjects affected / exposed                      | 0 / 85 (0.00%)      | 0 / 85 (0.00%)      | 2 / 42 (4.76%)      |
| occurrences (all)                                | 0                   | 0                   | 2                   |
| Abdominal pain upper                             |                     |                     |                     |
| subjects affected / exposed                      | 1 / 85 (1.18%)      | 2 / 85 (2.35%)      | 2 / 42 (4.76%)      |
| occurrences (all)                                | 1                   | 2                   | 2                   |
| Constipation                                     |                     |                     |                     |
| subjects affected / exposed                      | 0 / 85 (0.00%)      | 0 / 85 (0.00%)      | 2 / 42 (4.76%)      |
| occurrences (all)                                | 0                   | 0                   | 2                   |
| Infections and infestations                      |                     |                     |                     |
| Nasopharyngitis                                  |                     |                     |                     |
| subjects affected / exposed                      | 4 / 85 (4.71%)      | 3 / 85 (3.53%)      | 0 / 42 (0.00%)      |
| occurrences (all)                                | 4                   | 3                   | 0                   |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 06 November 2015 | <p>The substantial changes include:</p> <ol style="list-style-type: none"><li>1) The procedure for obtaining radiographic images was changed. A radiograph image of the index knee was added to the follow-up period to assess for potential changes in the index knee poststudy drug treatment. The requirement for a lateral view of hips was removed because it was considered not essential to the assessment of the progression of hip OA.</li><li>2) Inclusion Criteria 12 and 14 were revised. The list of highly effective forms of birth control was updated, and Inclusion Criteria 12 and 14 were updated to reflect current recommendations by the Clinical Trials Facilitation Group related to contraception in clinical trials.</li><li>3) The gastrointestinal protective strategy was expanded, adding explicit language to state that gastroprotective agents could be used at the investigators' discretion, considering the risk of serious gastrointestinal toxicity of naproxen, especially in older adults and patients treated with low dose aspirin for cardioprophylaxis.</li><li>4) Text was added regarding the absence of any evaluation of the test drug's phototoxic potential because specific phototoxicity studies have not been conducted for ASP7962. Although ASP7962 did not contain typical phototoxic structural moieties and the nonclinical data did not indicate a photosafety concern, based on the absorption peak at 305 nm, a phototoxicity potential for ASP7962 could not be excluded.</li></ol> <p>Nonsubstantial changes were made:</p> <ol style="list-style-type: none"><li>1) To update Sponsor contact information</li><li>2) To update footnote in schedule of assessments</li><li>3) To update Appendix 12.6.</li></ol>  |
| 26 July 2016     | <p>The substantial changes include: (continued from above)</p> <ol style="list-style-type: none"><li>5) Specification for exclusion of participants with severe knee malalignment or another jointrelated condition was updated. Due to the change of Inclusion Criterion 4, it was considered relevant to add severe malalignment to the exclusion criteria. Although malalignment does not appear to be an independent risk factor for RPOA, out of an abundance of caution, the Osteo IAC members recommended that patients with severe malalignment be excluded from the study. This was assessed through centrally read radiographs as well as clinical evaluation of the participant. It was recommended that, in case of acute subchondral insufficiency fracture, additional medical evaluation would be required before considering a participant for enrollment into this study.</li><li>6) The specification for exclusion of participants with specific shoulder medical history was updated. Based on a few cases of RPOA of the shoulder reported in the anti-NGF programs, there was a theoretical concern of RPOA of the shoulder. However, there is a lack of evidence to indicate which participants this might affect. As a history of conditions, such as rotator cuff diseases, was expected to be common among the patients, these types of condition were not to prohibit enrollment.</li><li>7) Exclusion Criterion12 was revised, stating that participants with intolerance or hypersensitivity to tramadol were allowed to enter the study if the participants accepted to limiting rescue medication to paracetamol.</li><li>8) Exclusion Criterion 17 was revised to allow the enrollment of participants with a history of cardiovascular disease whose condition was stable. Unexplained syncope was removed from the exclusion criterion. PR interval was increased from 210 to 240 ms.</li></ol> |

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| 26 July 2016 | <p>The substantial changes include: (continued from above)</p> <p>9) Exclusion Criterion 21 was revised, removing hepatitis B core antibodies (anti-HBc) test result from the exclusion criterion. HBsAg was considered a sufficient serologic test to assess presence of infection. A positive test result for anti-HBc in the presence of negative HBsAg suggests immunity due to natural infection. Active disease would be associated with increased liver tests and would be excluded due to Exclusion Criterion 19.</p> <p>10) Exclusion Criterion 23 was revised, limiting the exclusion of participants having previously received antibodies to NGF to 3 months prior to screening. A 3-month washout was considered sufficient not to interfere with any study endpoints or cause any safety concerns.</p> <p>11) Exclusion Criterion 23 and Prohibited Medications and Nonmedication Therapies were revised, reducing the use of intraarticular local anesthetics from 12 months to 3 months before screening. The reason was that there is no evidence that participants undergoing local anesthetic injection, such as lidocaine during a related single injection procedure, are at high risk of presentation of clinical chondral toxicity.</p> <p>12) The strength and use of cytochrome P450 inducers were specified, adding "strong" to cytochrome P450 inducers and "regularly" to be consistent with the wording of Exclusion Criterion 32.</p> <p>13) Study design was slightly revised, adding a section to allow reevaluation of participants who were not eligible under Version 2.0 of the protocol, but would be eligible based on the revised inclusion and exclusion criteria in Version 3.0 of the protocol. In case new radiographic assessments were deemed inappropriate, this was to be discussed first with the Medical Monitor.</p> <p>14) Laboratory assessments were modified, deleting benzodiazepines from drug and alcohol urine screening. Assessment of benzodiazepine use was not considered to impact participant safety or adherence to the protocol.</p> |
| 26 July 2016 | <p>Nonsubstantial changes were made: (continued from above)</p> <p>1) To update the contact details of key study personnel</p> <p>2) To update the abbreviations list</p> <p>3) To extend the planned study period</p> <p>4) To update the planned number of study centers</p> <p>5) To clarify the process for radiographic imaging</p> <p>6) To update the order of the secondary safety endpoints</p> <p>7) To update the statistical presentation of treatment-emergent adverse events (TEAEs)</p> <p>8) To add text regarding educational material for participants</p> <p>9) To update the schedule of assessments</p> <p>10) To update the Hospital Anxiety and Depression Scale (HADS)</p> <p>11) To update the physical examination section</p> <p>12) To update the Neuropathic Pain Symptom Inventory (NPSI)</p> <p>13) To update the reporting of serious adverse events (SAEs)</p> <p>14) To update the analysis of exploratory endpoints</p> <p>15) To update the statistical section on physical examination</p> <p>16) To delete a reference</p> <p>17) To update the table of questionnaires</p> <p>18) To include minor administrative-type changes.</p>   |

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| 26 July 2016 | <p>The substantial changes include:</p> <p>1) Inclusion Criterion 2 was revised, increasing the upper age limit from 75 to 80 years to allow participants aged 76 to 80 years to be entered in the study. The reason was that OA becomes increasingly prevalent with aging, and symptomatic OA affects many in their eighth decade. There was no evidence that ASP7962 should benefit older individuals to a lesser extent than those who are younger.</p> <p>2) Inclusion Criterion 8 was removed. This inclusion criterion required participants to have a mean daily index knee average pain score between <math>\geq 4</math> and <math>\leq 9</math> (on a 0 to 10 NRS). Pain criteria to enter the study were thus limited to the well-established WOMAC criteria for pain that are the standard for OA pain studies.</p> <p>3) Inclusion Criterion 6 was revised. The Kellgren-Lawrence grade at screening (based on central reading) was increased such that participants with Kellgren-Lawrence grade 4 were included as well. After a review of publically available information from the anti-NGF monoclonal antibody programs and discussion with external experts and key opinion leaders (with expertise in rheumatology, radiology and RPOA), the exclusion of Kellgren-Lawrence grade 4 was considered unnecessary as there was no evidence suggesting an increased risk of RPOA with Kellgren-Lawrence grade 4.</p> <p>4) Exclusion Criterion 4 was revised. If a participant was stable, treated and not experiencing clinical signs of concomitant diseases, the participant could be suitable as this should not impact safety or assessments within the study. For participants with diabetes mellitus, attaining a target HbA1c of <math>&lt; 6.5\%</math> to <math>7\%</math> can be challenging. For some participants the risks of intensive glycemic control may have outweighed the benefits and a less strict HbA1c cutoff seemed reasonable provided that, in the investigator's judgment, the participant was clinically stable. HbA1c was increased from <math>7.1\%</math> to <math>8.0\%</math> to allow a less strict surrogate for diabetes control.</p> |
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Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported