



Clinical trial results:

A Phase 2 Study to Evaluate the Efficacy and Safety of LY3462817 in Participants with Moderately to Severely Active Rheumatoid Arthritis Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2020-002673-10 |
| Trial protocol | CZ HU PL |
| Global end of trial date | 29 June 2022 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 12 July 2023 |
| First version publication date | 22 January 2023 |
| Version creation reason | <ul style="list-style-type: none">• New data added to full data set Final data to be posted |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | J1A-MC-KDAD |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|---------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04634253 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Trial Number: 17424 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Eli Lilly and Company |
| Sponsor organisation address | Lilly Corporate Center, Indianapolis, IN, United States, 46285 |
| Public contact | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly, |
| Scientific contact | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8772854559, |

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 June 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 29 June 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The reason for this study is to see if the study drug LY3462817 is safe and effective in participants with moderately to severely active rheumatoid arthritis (RA).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 04 January 2021 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Hungary: 28 |
| Country: Number of subjects enrolled | United States: 18 |
| Country: Number of subjects enrolled | Czechia: 4 |
| Country: Number of subjects enrolled | Poland: 18 |
| Country: Number of subjects enrolled | Mexico: 30 |
| Worldwide total number of subjects | 98 |
| EEA total number of subjects | 50 |

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) | 84 |

| | |
|---------------------|----|
| From 65 to 84 years | 14 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

No Text Available

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 | Subject, Investigator |

Arms

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

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

Arm description:

Participants received (0.9% sodium chloride solution) Placebo administered Intravenously.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

0.9% sodium chloride solution was administered as an IV infusion.

| | |
|------------------|------------------|
| Arm title | LY3462817 300 mg |
|------------------|------------------|

Arm description:

Participants received 300 milligrams (mg) of LY3462817 administered Intravenously.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | LY3462817 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

300 mg of LY3462817 administered as an IV infusion in 50 mg/mL in a 3-mL vial.

| | |
|------------------|------------------|
| Arm title | LY3462817 700 mg |
|------------------|------------------|

Arm description:

Participants received 700 mg of LY3462817 administered Intravenously.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | LY3462817 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

700 mg of LY3462817 administered as an IV infusion in 50 mg/mL in a 3-mL vial.

| Number of subjects in period 1 | Placebo | LY3462817 300 mg | LY3462817 700 mg |
|---------------------------------------|---------|------------------|------------------|
| Started | 24 | 25 | 49 |
| Completed | 22 | 23 | 46 |
| Not completed | 2 | 2 | 3 |
| Consent withdrawn by subject | 1 | - | 3 |
| Physician decision | - | 1 | - |
| Adverse event, non-fatal | 1 | 1 | - |

Baseline characteristics

Reporting groups

| | |
|---|------------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received (0.9% sodium chloride solution) Placebo administered Intravenously. | |
| Reporting group title | LY3462817 300 mg |
| Reporting group description: | |
| Participants received 300 milligrams (mg) of LY3462817 administered Intravenously. | |
| Reporting group title | LY3462817 700 mg |
| Reporting group description: | |
| Participants received 700 mg of LY3462817 administered Intravenously. | |

| Reporting group values | Placebo | LY3462817 300 mg | LY3462817 700 mg |
|--|---------|------------------|------------------|
| Number of subjects | 24 | 25 | 49 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 55.8 | 50.1 | 50.5 |
| standard deviation | ± 11.1 | ± 15.8 | ± 11.2 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 19 | 20 | 43 |
| Male | 5 | 5 | 6 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 7 | 10 | 13 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 2 |
| White | 17 | 15 | 34 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| Hungary | 8 | 5 | 15 |
| United States | 4 | 5 | 9 |

| | | | |
|---------|---|----|----|
| Czechia | 0 | 3 | 1 |
| Poland | 5 | 2 | 11 |
| Mexico | 7 | 10 | 13 |

| Reporting group values | Total | | |
|---|-------|--|--|
| Number of subjects | 98 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 82 | | |
| Male | 16 | | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 30 | | |
| Asian | 0 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| Black or African American | 2 | | |
| White | 66 | | |
| More than one race | 0 | | |
| Unknown or Not Reported | 0 | | |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| Hungary | 28 | | |
| United States | 18 | | |
| Czechia | 4 | | |
| Poland | 18 | | |
| Mexico | 30 | | |

End points

End points reporting groups

| | |
|---|------------------|
| Reporting group title | Placebo |
| Reporting group description: Participants received (0.9% sodium chloride solution) Placebo administered Intravenously. | |
| Reporting group title | LY3462817 300 mg |
| Reporting group description: Participants received 300 milligrams (mg) of LY3462817 administered Intravenously. | |
| Reporting group title | LY3462817 700 mg |
| Reporting group description: Participants received 700 mg of LY3462817 administered Intravenously. | |

Primary: Change from Baseline on the Disease Activity Score Modified to Include the 28 Diarthrodial Joint Count–High-Sensitivity C-Reactive Protein (DAS28-hsCRP)

| | |
|-----------------|--|
| End point title | Change from Baseline on the Disease Activity Score Modified to Include the 28 Diarthrodial Joint Count–High-Sensitivity C-Reactive Protein (DAS28-hsCRP) |
|-----------------|--|

End point description:

Disease Activity Score (DAS) based on a 28 joint count hsCRP consisted of composite numerical score of the following variables: tender joint count (TJC28), swollen joint count (SJC28), hsCRP (mg/mL), and participant's global assessment of disease activity. DAS28-hsCRP was calculated using following formula: $\text{DAS28-hsCRP} = 0.56 \times \sqrt{\text{TJC28}} + 0.28 \times \sqrt{\text{SJC28}} + 0.014 \times \text{participant's global assessment of disease activity} + 0.36 \times \ln(\text{hsCRP} + 1) + 0.96$. Scores ranged 1.0-9.4, where lower scores indicated less disease activity. Least Square Mean (LS Mean) was calculated using mixed model repeated measures (MMRM) with treatment, strata (previous RA therapy population), baseline value, visit, treatment-by-visit interaction as fixed factors. Analysis Population Description (APD): All randomized participants who received at least one dose and had data for DAS28-hsCRP

| | |
|---|---------|
| End point type | Primary |
| End point timeframe: Baseline, Week 12 | |

| End point values | Placebo | LY3462817 300 mg | LY3462817 700 mg | |
|-------------------------------------|-----------------|------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 22 | 42 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -0.99 (± 0.261) | -1.88 (± 0.249) | -2.09 (± 0.184) | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Change from Baseline on the DAS28-hsCRP |
| Comparison groups | Placebo v LY3462817 300 mg |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 42 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.017 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean |
| Point estimate | -0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.6 |
| upper limit | -0.16 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.361 |

| | |
|---|---|
| Statistical analysis title | Change from Baseline on the DAS28-hsCRP |
| Comparison groups | Placebo v LY3462817 700 mg |
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean |
| Point estimate | -1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.73 |
| upper limit | -0.46 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.32 |

Secondary: Percentage of Participants Achieving 20% Improvement in American College of Rheumatology Criteria (ACR20)

| | |
|-----------------|---|
| End point title | Percentage of Participants Achieving 20% Improvement in American College of Rheumatology Criteria (ACR20) |
|-----------------|---|

End point description:

ACR responders are participants with at least 20% improvement from baseline for tender joint count (TJC), swollen joint count (SJC), and at least 3 of the 5 remaining core set measures: Health Assessment Questionnaire-Disability Index (HAQ-DI) which measures participants perceived degree of difficulty performing daily activities, acute phase reactant as measured by hsCRP, Patient's Assessment of Pain-Visual Analog Scale (Pain-VAS), Patient's Global Assessment of Disease Activity (PaGADA_VAS), and Physician's Global Assessment of Disease Activity (PhGADA_VAS).

APD: All randomized participants.

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

End point timeframe:

Week 12

| End point values | Placebo | LY3462817 300 mg | LY3462817 700 mg | |
|-----------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 24 | 25 | 49 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 41.7 (21.9 to 61.4) | 44.0 (24.5 to 63.5) | 71.4 (58.8 to 84.1) | |

Statistical analyses

| Statistical analysis title | Percentage of Participants Achieving ACR20 |
|---|--|
| Comparison groups | Placebo v LY3462817 300 mg |
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.997 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.29 |
| upper limit | 3.44 |

| Statistical analysis title | Percentage of Participants Achieving ACR20 |
|---|--|
| Comparison groups | Placebo v LY3462817 700 mg |
| Number of subjects included in analysis | 73 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.032 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.11 |
| upper limit | 10.4 |

Secondary: Percentage of Participants Achieving 70% Improvement in American

College of Rheumatology Criteria (ACR70)

| | |
|-----------------|---|
| End point title | Percentage of Participants Achieving 70% Improvement in American College of Rheumatology Criteria (ACR70) |
|-----------------|---|

End point description:

ACR responders are participants with at least 70% improvement from baseline for tender joint count (TJC), swollen joint count (SJC), and at least 3 of the 5 remaining core set measures: Health Assessment Questionnaire-Disability Index (HAQ-DI) which measures participants perceived degree of difficulty performing daily activities, acute phase reactant as measured by hsCRP, Patient's Assessment of Pain-Visual Analog Scale (Pain-VAS), Patient's Global Assessment of Disease Activity (PaGADA_VAS), and Physician's Global Assessment of Disease Activity (PhGADA_VAS).

APD: All randomized participants.

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

End point timeframe:

Week 12

| End point values | Placebo | LY3462817 300 mg | LY3462817 700 mg | |
|-----------------------------------|--------------------|------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 24 | 25 | 49 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 16.7 (1.8 to 31.6) | 4.0 (0 to 11.7) | 20.4 (9.1 to 31.7) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Percentage of Participants Achieving ACR70 |
| Comparison groups | Placebo v LY3462817 300 mg |
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.235 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.04 |
| upper limit | 2.25 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Percentage of Participants Achieving ACR70 |
| Comparison groups | Placebo v LY3462817 700 mg |

| | |
|---|----------------------|
| Number of subjects included in analysis | 73 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.661 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.33 |
| upper limit | 5.61 |

Secondary: Percentage of Participants Achieving 50% Improvement in American College of Rheumatology Criteria (ACR50)

| | |
|-----------------|---|
| End point title | Percentage of Participants Achieving 50% Improvement in American College of Rheumatology Criteria (ACR50) |
|-----------------|---|

End point description:

ACR responders are participants with at least 50% improvement from baseline for tender joint count (TJC), swollen joint count (SJC), and at least 3 of the 5 remaining core set measures: Health Assessment Questionnaire-Disability Index (HAQ-DI) which measures participants perceived degree of difficulty performing daily activities, acute phase reactant as measured by hsCRP, Patient's Assessment of Pain-Visual Analog Scale (Pain-VAS), Patient's Global Assessment of Disease Activity (PaGADA_VAS), and Physician's Global Assessment of Disease Activity (PhGADA_VAS).

APD: All randomized participants.

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

End point timeframe:

Week 12

| End point values | Placebo | LY3462817 300 mg | LY3462817 700 mg | |
|-----------------------------------|--------------------|--------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 24 | 25 | 49 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 20.8 (4.6 to 37.1) | 20.0 (4.3 to 35.7) | 38.8 (25.1 to 52.4) | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Percentage of Participants Achieving ACR50 |
| Comparison groups | Placebo v LY3462817 300 mg |

| | |
|---|----------------------|
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.965 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.22 |
| upper limit | 4.28 |

| | |
|---|--|
| Statistical analysis title | Percentage of Participants Achieving ACR50 |
| Comparison groups | Placebo v LY3462817 700 mg |
| Number of subjects included in analysis | 73 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.098 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 10.33 |

Secondary: Change from Baseline for Mean Simplified Disease Activity Index (SDAI)

| | |
|-----------------|--|
| End point title | Change from Baseline for Mean Simplified Disease Activity Index (SDAI) |
|-----------------|--|

End point description:

The SDAI is a tool for measurement of disease activity in RA that integrates measures of physical examination, acute phase response, patient self-assessment, and evaluator assessment. The SDAI is calculated by adding together scores from 1) TJC28 (0 to 28), 2) SJC28 (0 to 28), 3) acute phase response using C-reactive protein (0.1 to 10.0 mg/dL), 4) Patient's Global Assessment of Disease Activity using VAS (0 to 10 cm), and 5) Physician's Global Assessment of Disease Activity using VAS (0 to 10 cm). Total Score scale range is 0 (remission) to 86 (high disease activity). LS Mean was calculated using mixed model repeated measures (MMRM) with treatment, strata (previous RA therapy population), baseline value, visit, treatment-by-visit interaction as fixed factors.

APD: All randomized participants who received at least one dose and had data for SDAI.

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

End point timeframe:

Baseline, Week 12

| End point values | Placebo | LY3462817 300 mg | LY3462817 700 mg | |
|-------------------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 21 | 42 | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -13.80 (\pm 2.664) | -25.06 (\pm 2.571) | -26.90 (\pm 1.880) | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Change from Baseline for SDAI |
| Comparison groups | Placebo v LY3462817 300 mg |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -11.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18.65 |
| upper limit | -3.87 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.71 |

| | |
|---|-------------------------------|
| Statistical analysis title | Change from Baseline for SDAI |
| Comparison groups | Placebo v LY3462817 700 mg |
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -13.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.61 |
| upper limit | -6.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.265 |

Secondary: Change from Baseline for Mean Clinical Disease Activity Index (CDAI)

| | |
|--|--|
| End point title | Change from Baseline for Mean Clinical Disease Activity Index (CDAI) |
| End point description: | |
| <p>The CDAI is a tool for measurement of disease activity in RA that does not require a laboratory component and was scored by the investigative site. It integrates TJC28 (scored 0-28 with higher scores indicating higher disease activity), SJC28 (scored 0-28 with higher scores indicating higher disease activity), Patient's Global Assessment of Disease Activity (scored on a visual analogue scale from 0-10 cm with higher scores indicating higher disease activity), and Physician's Global Assessment of Disease Activity (scored on a visual analogue scale from 0-10 cm with higher scores indicating higher disease activity). The CDAI is calculated by summing the values of the 4 components. CDAI scores range from 0 to 76; lower scores indicated lower disease activity. A negative change from baseline indicates improvement in condition. LS Mean was calculated using MMRM with treatment, strata (previous RA therapy population), baseline value, visit, treatment-by-visit interaction as fixed factors.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 12 | |

| End point values | Placebo | LY3462817 300 mg | LY3462817 700 mg | |
|-------------------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 21 | 44 | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -13.75 (\pm 2.709) | -24.06 (\pm 2.628) | -25.51 (\pm 1.854) | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Change from Baseline for CDAI |
| Comparison groups | Placebo v LY3462817 300 mg |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.008 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -10.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.83 |
| upper limit | -2.77 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.782 |

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | Change from Baseline for CDAI |
| Comparison groups | Placebo v LY3462817 700 mg |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 64 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -11.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18.29 |
| upper limit | -5.22 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.282 |

Secondary: Change From Baseline in Mental Component Score (MCS), Physical Component Score (PCS) of the Medical Outcomes Study 36-Item Short Form Health Survey Version 2 Acute (SF-36v2 Acute)

| | |
|-----------------|---|
| End point title | Change From Baseline in Mental Component Score (MCS), Physical Component Score (PCS) of the Medical Outcomes Study 36-Item Short Form Health Survey Version 2 Acute (SF-36v2 Acute) |
|-----------------|---|

End point description:

The SF-36 is a health-related survey that assesses participant's health status and consists of 36 questions covering 8 health domains: physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health, mental health, social functioning, and vitality. The 8 domains are combined to form 2 component scores mental (MCS) and physical (PCS). MCS consisted of social functioning, vitality, mental health, and role-emotional scales. PCS consisted of physical functioning, bodily pain, role-physical, and general health scales. Each domain is scored by summing the individual items and transforming the scores into a 0 to 100 scale with higher scores indicating better health status. LS mean was determined by ANCOVA with factors for treatment and previous RA therapy population included as fixed factors,

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 12 | |

| End point values | Placebo | LY3462817 300 mg | LY3462817 700 mg | |
|-------------------------------------|-----------------|------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 21 | 23 | 47 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| PCS | 5.01 (± 1.711) | 7.03 (± 1.633) | 6.43 (± 1.165) | |
| MCS | 3.48 (± 1.715) | 0.55 (± 1.630) | 4.64 (± 1.166) | |

Statistical analyses

| | |
|---|------------------------------|
| Statistical analysis title | Mental Component Score (MCS) |
| Comparison groups | Placebo v LY3462817 300 mg |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.218 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.63 |
| upper limit | 1.77 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.365 |

| | |
|---|------------------------------|
| Statistical analysis title | Mental Component Score (MCS) |
| Comparison groups | Placebo v LY3462817 700 mg |
| Number of subjects included in analysis | 68 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.578 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.95 |
| upper limit | 5.26 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.065 |

| | |
|---|--------------------------------|
| Statistical analysis title | Physical Component Score (PCS) |
| Comparison groups | Placebo v LY3462817 300 mg |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.396 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 2.02 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.69 |
| upper limit | 6.73 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.368 |

Secondary: Pharmacokinetics (PK): Observed Concentration of LY3462817

| | |
|-----------------|--|
| End point title | Pharmacokinetics (PK): Observed Concentration of |
|-----------------|--|

End point description:

PK: Observed Concentration of LY3462817

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

End point timeframe:

Week 12

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK analysis is for LY3462817

| | | | | |
|----------------------------------|----------------------|-----------------------|--|--|
| End point values | LY3462817 300 mg | LY3462817 700 mg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 49 | | |
| Units: nanograms per milliliter | | | | |
| median (confidence interval 95%) | 7970 (1290 to 17100) | 15600 (1820 to 36600) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline, up to Week 12

Adverse event reporting additional description:

All randomized participants who received at least one dose of study drug. Gender specific events only occurring in male or female participants have had the number of participants At Risk adjusted accordingly.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 25.0 |

Reporting groups

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

Reporting group description: -

| | |
|-----------------------|------------------|
| Reporting group title | LY3462817 700 mg |
|-----------------------|------------------|

Reporting group description: -

| | |
|-----------------------|------------------|
| Reporting group title | LY3462817 300 mg |
|-----------------------|------------------|

Reporting group description: -

| Serious adverse events | Placebo | LY3462817 700 mg | LY3462817 300 mg |
|---|----------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 49 (2.04%) | 0 / 25 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Endocrine disorders | | | |
| hypothyroidism | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 49 (2.04%) | 0 / 25 (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: 0 %

| Non-serious adverse events | Placebo | LY3462817 700 mg | LY3462817 300 mg |
|---|-----------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 24 (37.50%) | 13 / 49 (26.53%) | 8 / 25 (32.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|--|--|--|--|
| b-cell lymphoma alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | 0 / 49 (0.00%) 0 | 0 / 25 (0.00%) 0 |
| Investigations weight increased alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 0 / 49 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Vascular disorders hypertension alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 2 / 24 (8.33%) 2 | 0 / 49 (0.00%) 0 | 0 / 25 (0.00%) 0 |
| Surgical and medical procedures tooth extraction alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | 0 / 49 (0.00%) 0 | 0 / 25 (0.00%) 0 |
| Nervous system disorders allodynia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) dizziness alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) headache alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) hypoesthesia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 0 / 24 (0.00%) 0 0 / 24 (0.00%) 0 0 / 24 (0.00%) 0 | 0 / 49 (0.00%) 0 0 / 49 (0.00%) 0 1 / 49 (2.04%) 1 1 / 49 (2.04%) 1 | 1 / 25 (4.00%) 1 1 / 25 (4.00%) 1 0 / 25 (0.00%) 0 0 / 25 (0.00%) 0 |

| | | | |
|---|---|---|---|
| General disorders and administration site conditions fatigue alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) pyrexia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 0 / 24 (0.00%) 0 | 0 / 49 (0.00%) 0 1 / 49 (2.04%) 1 | 0 / 25 (0.00%) 0 0 / 25 (0.00%) 0 |
| Gastrointestinal disorders diarrhoea alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) nausea alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) vomiting alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 0 / 24 (0.00%) 0 0 / 24 (0.00%) 0 | 1 / 49 (2.04%) 1 4 / 49 (8.16%) 4 1 / 49 (2.04%) 1 | 0 / 25 (0.00%) 0 0 / 25 (0.00%) 0 0 / 25 (0.00%) 0 |
| Skin and subcutaneous tissue disorders dermatitis atopic alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) onychoclasia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) pruritus alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 1 / 24 (4.17%) 1 1 / 24 (4.17%) 1 | 1 / 49 (2.04%) 1 0 / 49 (0.00%) 0 1 / 49 (2.04%) 3 | 0 / 25 (0.00%) 0 0 / 25 (0.00%) 0 0 / 25 (0.00%) 0 |

| | | | |
|---|---|----------------|----------------|
| Musculoskeletal and connective tissue disorders | | | |
| | arthralgia | | |
| | alternative dictionary used: MedDRA 25.0 | | |
| | subjects affected / exposed | 0 / 24 (0.00%) | 1 / 49 (2.04%) |
| | occurrences (all) | 0 | 1 |
| | | | 0 / 25 (0.00%) |
| | back pain | | |
| | alternative dictionary used: MedDRA 25.0 | | |
| | subjects affected / exposed | 0 / 24 (0.00%) | 1 / 49 (2.04%) |
| | occurrences (all) | 0 | 1 |
| | | | 0 / 25 (0.00%) |
| | osteoarthritis | | |
| | alternative dictionary used: MedDRA 25.0 | | |
| | subjects affected / exposed | 0 / 24 (0.00%) | 1 / 49 (2.04%) |
| | occurrences (all) | 0 | 1 |
| | | | 0 / 25 (0.00%) |
| Infections and infestations | rheumatoid arthritis | | |
| | alternative dictionary used: MedDRA 25.0 | | |
| | subjects affected / exposed | 1 / 24 (4.17%) | 0 / 49 (0.00%) |
| | occurrences (all) | 1 | 0 |
| | | | 0 / 25 (0.00%) |
| | | | |
| | covid-19 | | |
| | alternative dictionary used: MedDRA 25.0 | | |
| | subjects affected / exposed | 0 / 24 (0.00%) | 1 / 49 (2.04%) |
| | occurrences (all) | 0 | 1 |
| | | | 1 / 25 (4.00%) |
| | gastroenteritis | | |
| | alternative dictionary used: MedDRA 25.0 | | |
| | subjects affected / exposed | 0 / 24 (0.00%) | 0 / 49 (0.00%) |
| | occurrences (all) | 0 | 0 |
| | | | 1 / 25 (4.00%) |
| | helicobacter infection | | |
| | alternative dictionary used: MedDRA 25.0 | | |
| | subjects affected / exposed | 0 / 24 (0.00%) | 0 / 49 (0.00%) |
| | occurrences (all) | 0 | 0 |
| | | | 1 / 25 (4.00%) |
| | herpes simplex | | |
| | alternative dictionary used: MedDRA 25.0 | | |
| | subjects affected / exposed | 1 / 24 (4.17%) | 0 / 49 (0.00%) |
| | occurrences (all) | 1 | 0 |
| | | | 0 / 25 (0.00%) |
| | mastitis | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

| | | | |
|--|----------------|----------------|----------------|
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 49 (0.00%) | 1 / 25 (4.00%) |
| occurrences (all) | 0 | 0 | 1 |
| nasopharyngitis | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 1 / 49 (2.04%) | 2 / 25 (8.00%) |
| occurrences (all) | 1 | 1 | 2 |
| rhinitis | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 49 (2.04%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| sinusitis | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 49 (0.00%) | 1 / 25 (4.00%) |
| occurrences (all) | 0 | 0 | 1 |
| skin bacterial infection | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 49 (0.00%) | 1 / 25 (4.00%) |
| occurrences (all) | 0 | 0 | 1 |
| tooth abscess | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 49 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| upper respiratory tract infection | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 49 (2.04%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| urinary tract infection | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 49 (2.04%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| upper respiratory tract infection bacterial | | | |
| alternative dictionary used: MedDRA 25.0 | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 49 (2.04%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| vulvovaginal candidiasis | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed ^[1] | 0 / 19 (0.00%) | 1 / 43 (2.33%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| diabetes mellitus | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 49 (2.04%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| dyslipidaemia | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | 1 / 49 (2.04%) | 0 / 25 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| hyperglycaemia | | | |
| alternative dictionary used: MedDRA 25.0 | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 49 (2.04%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Gender specific events only occurring in male or female participants have had the number of participants At Risk adjusted accordingly.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 21 September 2020 | Protocol Amendment (a) <ul style="list-style-type: none">• Participants on placebo will not be allowed to crossover to LY3462817 at any point during the study.• Added requirement of an Interim Analysis of Study KDAC data collected prior to proceeding to Period 2.• Standard of Care (SOC) therapy to be allowed to begin at Week 14.• All participants on placebo will receive SOC starting at Week 14 (Visit 7).• Removed Rescue Therapy wording• Patients who do not achieve Low Disease Activity will be removed from LY3462817 and switched to standard of care.• Patients who do achieve Low Disease Activity will be allowed LY3462817 until week 24. |
| 11 December 2020 | Protocol amendment (b): The protocol was amended to clarify study procedures and statistical considerations. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No adjustment for multiplicity was made. For assessments beyond the primary endpoint, nominal p-values are reported.

Notes: