



Clinical trial results:

Protocol I8B-MC-ITRN

A Prospective, Randomized, Double-Blind Comparison of LY900014 to Insulin Lispro, Both in Combination with Insulin Glargine or Insulin Degludec in Adults with Type 2 Diabetes

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-005357-12 |
| Trial protocol | HU ES SK DE IT |
| Global end of trial date | 13 March 2019 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 29 March 2020 |
| First version publication date | 29 March 2020 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | I8B-MC-ITRN |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|---------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03214380 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Trial Number: 16314 |

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 | 13 March 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 March 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to compare LY900014 to insulin lispro, both in combination with insulin glargine or insulin degludec, in participants with type 2 diabetes (T2D).

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:

Participants were required to use the same basal insulin regimen throughout the study with allowed regimens as follows: 100 U/mL (U-100) basal insulin glargine given SC once or twice daily or U-100 or 200 U/mL (U-200) insulin degludec given SC once daily. Participants may have continued the use of metformin and/or a sodium glucose cotransporter 2 inhibitor (SGLT-2) during the lead-in and treatment phase.

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 14 July 2017 |
| 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 | Argentina: 56 |
| Country: Number of subjects enrolled | Puerto Rico: 14 |
| Country: Number of subjects enrolled | Hungary: 28 |
| Country: Number of subjects enrolled | United States: 187 |
| Country: Number of subjects enrolled | Japan: 93 |
| Country: Number of subjects enrolled | India: 100 |
| Country: Number of subjects enrolled | Russian Federation: 50 |
| Country: Number of subjects enrolled | Spain: 30 |
| Country: Number of subjects enrolled | Korea, Republic of: 69 |
| Country: Number of subjects enrolled | Taiwan: 33 |
| Country: Number of subjects enrolled | Italy: 9 |
| Country: Number of subjects enrolled | Mexico: 45 |
| Country: Number of subjects enrolled | Slovakia: 28 |
| Country: Number of subjects enrolled | Australia: 15 |
| Country: Number of subjects enrolled | Germany: 40 |
| Country: Number of subjects enrolled | Czech Republic: 40 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 837 |
| EEA total number of subjects | 175 |

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) | 530 |
| From 65 to 84 years | 306 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

Maximum Extended Enrollment (MEE) cohorts are implemented in certain countries to meet regulatory requirements for submission. Data from MEE cohort will not be incorporated into the analysis of the global study cohort.

Pre-assignment

Screening details:

The purpose of the Lead-in Period was to titrate basal insulin prior to randomization. Participants were then randomized to receive Insulin lispro (Humalog) or LY900014 in the Treatment Period (Period 2).

Period 1

| | |
|------------------------------|-----------------------------|
| Period 1 title | Lead-in |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|----------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Insulin Lispro (Humalog) Lead-In |

Arm description:

100 U/mL Insulin lispro(Humalog) given SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Insulin Lispro |
| Investigational medicinal product code | |
| Other name | Humalog |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

100 U/mL Insulin lispro given SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily. Prandial insulin doses were individualized and titrated according to protocol-defined targets.

| | |
|------------------|--|
| Arm title | Insulin Lispro (Humalog) Lead-In Maximum Extended Enrollment |
|------------------|--|

Arm description:

100 U/mL Insulin lispro (Humalog) SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Insulin Lispro |
| Investigational medicinal product code | |
| Other name | Humalog |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

100 U/mL Insulin lispro given SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily. Prandial insulin doses were individualized and titrated according to protocol-defined targets.

| Number of subjects in period 1 | Insulin Lispro (Humalog) Lead-In | Insulin Lispro (Humalog) Lead-In Maximum Extended Enrollment |
|--|----------------------------------|--|
| | | |
| Started | 750 | 183 |
| Received at least 1 dose Lead-in Insulin | 750 | 183 |
| Completed | 673 | 164 |
| Not completed | 77 | 19 |
| Physician decision | 6 | - |
| Consent withdrawn by subject | 41 | 14 |
| Adverse event, non-fatal | 3 | 1 |
| Non compliance | 1 | - |
| Eligibility criteria | 3 | - |
| Natural disaster | 9 | - |
| Participant schedule | 2 | - |
| Lost to follow-up | 4 | 1 |
| Family emergency | 1 | - |
| Protocol deviation | 7 | 3 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Treatment Period |
| Is this the baseline period? | Yes ^[1] |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Insulin Lispro (Humalog) |

Arm description:

100 U/mL Insulin lispro given SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Insulin Lispro |
| Investigational medicinal product code | |
| Other name | Humalog |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

100 U/mL Insulin lispro given SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily. Prandial insulin doses were individualized and titrated according to protocol-defined targets.

| | |
|------------------|----------|
| Arm title | LY900014 |
|------------------|----------|

Arm description:

100 U/mL LY900014 SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily.

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | LY900014 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

LY900014 given subcutaneously (SC) with each meal with either 100 U/mL (U-100) basal insulin glargine given SC once or twice daily or U-100 or 200 U/mL (U-200) insulin degludec given SC once daily. Prandial insulin doses were individualized and titrated according to protocol-defined targets.

| | |
|------------------|--|
| Arm title | Insulin Lispro (Humalog) Maximum Extended Enrollment (MEE) |
|------------------|--|

Arm description:

100 U/mL Insulin lispro (Humalog) SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Insulin Lispro |
| Investigational medicinal product code | |
| Other name | Humalog |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

100 U/mL Insulin lispro given SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily. Prandial insulin doses were individualized and titrated according to protocol-defined targets.

| | |
|------------------|----------------|
| Arm title | LY900014 (MEE) |
|------------------|----------------|

Arm description:

100 U/mL LY900014 SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily.

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | LY900014 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

LY900014 given subcutaneously (SC) with each meal with either 100 U/mL (U-100) basal insulin glargine given SC once or twice daily or U-100 or 200 U/mL (U-200) insulin degludec given SC once daily. Prandial insulin doses were individualized and titrated according to protocol-defined targets.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The Lead-in Period (Period 1) was used to titrate basal insulin, to allow the participants to reach the target fasting blood glucose (FBG) by the end of this period, prior to randomization. Baseline analysis population is based on all randomized participants. Participants were randomized to Insulin Lispro or LY900014 in Period 2.

| Number of subjects in period 2 | Insulin Lispro (Humalog) | LY900014 | Insulin Lispro (Humalog) Maximum Extended Enrollment (MEE) |
|--|--------------------------|----------|--|
| | | | |
| Started | 337 | 336 | 82 |
| Received at least 1 dose of study drug | 337 | 336 | 82 |

| | | | |
|--------------------------------|-----|-----|----|
| Completed | 319 | 320 | 73 |
| Not completed | 18 | 16 | 9 |
| Consent withdrawn by subject | 10 | 8 | 7 |
| Non-Compliance with Study Drug | - | - | 1 |
| Adverse event, non-fatal | 1 | 1 | 1 |
| Death | 1 | 2 | - |
| Participant schedule | - | 1 | - |
| Treatment interruption | - | 1 | - |
| Lost to follow-up | 6 | 3 | - |

| | |
|--|----------------|
| Number of subjects in period 2 | LY900014 (MEE) |
| Started | 82 |
| Received at least 1 dose of study drug | 82 |
| Completed | 71 |
| Not completed | 11 |
| Consent withdrawn by subject | 11 |
| Non-Compliance with Study Drug | - |
| Adverse event, non-fatal | - |
| Death | - |
| Participant schedule | - |
| Treatment interruption | - |
| Lost to follow-up | - |

Baseline characteristics

Reporting groups

| | |
|--|--|
| Reporting group title | Insulin Lispro (Humalog) |
| Reporting group description: 100 U/mL Insulin lispro given SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily. | |
| Reporting group title | LY900014 |
| Reporting group description: 100 U/mL LY900014 SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily. | |
| Reporting group title | Insulin Lispro (Humalog) Maximum Extended Enrollment (MEE) |
| Reporting group description: 100 U/mL Insulin lispro (Humalog) SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily. | |
| Reporting group title | LY900014 (MEE) |
| Reporting group description: 100 U/mL LY900014 SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily. | |

| Reporting group values | Insulin Lispro (Humalog) | LY900014 | Insulin Lispro (Humalog) Maximum Extended Enrollment (MEE) |
|---|--------------------------|----------|--|
| Number of subjects | 337 | 336 | 82 |
| Age categorical Units: Subjects | | | |
| Age continuous | | | |
| All randomized participants. | | | |
| Units: years | | | |
| arithmetic mean | 61.0 | 60.2 | 56.6 |
| standard deviation | ± 9.2 | ± 9.4 | ± 9.4 |
| Gender categorical | | | |
| All randomized participants. | | | |
| Units: Subjects | | | |
| Female | 162 | 152 | 47 |
| Male | 175 | 184 | 35 |
| Race (NIH/OMB) | | | |
| All randomized participants. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 3 | 1 | 0 |
| Asian | 81 | 83 | 70 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 0 |
| Black or African American | 16 | 14 | 0 |
| White | 229 | 233 | 12 |
| More than one race | 6 | 5 | 0 |
| Unknown or Not Reported | 1 | 0 | 0 |
| Region of Enrollment | | | |
| All randomized participants. | | | |

| | | | |
|------------------------------|--------|--------|--------|
| Units: Subjects | | | |
| Argentina | 29 | 27 | 0 |
| Puerto Rico | 7 | 7 | 0 |
| Hungary | 13 | 15 | 0 |
| United States | 95 | 92 | 0 |
| Czechia | 20 | 20 | 0 |
| Japan | 46 | 47 | 0 |
| India | 9 | 7 | 40 |
| Russia | 14 | 13 | 11 |
| Spain | 16 | 14 | 0 |
| South Korea | 16 | 16 | 21 |
| Taiwan | 7 | 8 | 9 |
| Italy | 4 | 5 | 0 |
| Mexico | 21 | 22 | 1 |
| Slovakia | 14 | 14 | 0 |
| Australia | 7 | 8 | 0 |
| Germany | 19 | 21 | 0 |
| Hemoglobin A1c | | | |
| All randomized participants. | | | |
| Units: percentage of HbA1c | | | |
| arithmetic mean | 7.31 | 7.27 | 7.53 |
| standard deviation | ± 0.72 | ± 0.68 | ± 0.69 |

| | | | |
|-------------------------------|----------------|-------|--|
| Reporting group values | LY900014 (MEE) | Total | |
| Number of subjects | 82 | 837 | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|--------|-----|--|
| Age continuous | | | |
| All randomized participants. | | | |
| Units: years | | | |
| arithmetic mean | 57.2 | | |
| standard deviation | ± 10.1 | - | |
| Gender categorical | | | |
| All randomized participants. | | | |
| Units: Subjects | | | |
| Female | 27 | 388 | |
| Male | 55 | 449 | |
| Race (NIH/OMB) | | | |
| All randomized participants. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 4 | |
| Asian | 69 | 303 | |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | |
| Black or African American | 0 | 30 | |
| White | 13 | 487 | |
| More than one race | 0 | 11 | |
| Unknown or Not Reported | 0 | 1 | |
| Region of Enrollment | | | |
| All randomized participants. | | | |
| Units: Subjects | | | |

| | | | |
|------------------------------|--------|-----|--|
| Argentina | 0 | 56 | |
| Puerto Rico | 0 | 14 | |
| Hungary | 0 | 28 | |
| United States | 0 | 187 | |
| Czechia | 0 | 40 | |
| Japan | 0 | 93 | |
| India | 44 | 100 | |
| Russia | 12 | 50 | |
| Spain | 0 | 30 | |
| South Korea | 16 | 69 | |
| Taiwan | 9 | 33 | |
| Italy | 0 | 9 | |
| Mexico | 1 | 45 | |
| Slovakia | 0 | 28 | |
| Australia | 0 | 15 | |
| Germany | 0 | 40 | |
| Hemoglobin A1c | | | |
| All randomized participants. | | | |
| Units: percentage of HbA1c | | | |
| arithmetic mean | 7.67 | | |
| standard deviation | ± 0.89 | - | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Insulin Lispro (Humalog) Lead-In |
| Reporting group description: 100 U/mL Insulin lispro(Humalog) given SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily. | |
| Reporting group title | Insulin Lispro (Humalog) Lead-In Maximum Extended Enrollment |
| Reporting group description: 100 U/mL Insulin lispro (Humalog) SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily. | |
| Reporting group title | Insulin Lispro (Humalog) |
| Reporting group description: 100 U/mL Insulin lispro given SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily. | |
| Reporting group title | LY900014 |
| Reporting group description: 100 U/mL LY900014 SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily. | |
| Reporting group title | Insulin Lispro (Humalog) Maximum Extended Enrollment (MEE) |
| Reporting group description: 100 U/mL Insulin lispro (Humalog) SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily. | |
| Reporting group title | LY900014 (MEE) |
| Reporting group description: 100 U/mL LY900014 SC with each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily. | |
| Subject analysis set title | Insulin Lispro (Humalog) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Insulin lispro given SC with each meal with either U-100 basal insulin glargine given SC once or twice daily or U-100 or U-200 insulin degludec given SC once daily. | |
| Subject analysis set title | LY900014 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: LY900014 given subcutaneously (SC) with each meal with either 100 U/mL (U-100) basal insulin glargine given SC once or twice daily or U-100 or 200 U/mL (U-200) insulin degludec given SC once daily. | |

Primary: Change from Baseline in Hemoglobin A1c (HbA1c) Efficacy Estimand at Week 26

| | |
|--|---|
| End point title | Change from Baseline in Hemoglobin A1c (HbA1c) Efficacy Estimand at Week 26 |
| End point description: Change from baseline in HbA1c was performed using mixed model repeated measure (MMRM) including fixed class effects of treatment, strata (pooled country, type of basal insulin, and number of prandial doses at study entry), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline value. The efficacy estimand included participant data when baseline and at least one post-baseline measurement were available prior to permanent discontinuation of study drug. | |
| Analysis Population Description (APD): All randomized participants with baseline and at least one post-baseline HbA1c data. As pre-specified in the analysis plan, outcome measures will not be reported for the Maximum Extended Enrollment (MEE) arms/groups but only for the main global study arms/groups. | |
| End point type | Primary |

End point timeframe:

Baseline, Week 26

| | | | | |
|-------------------------------------|--------------------------|----------------------|--|--|
| End point values | Insulin Lispro (Humalog) | LY900014 | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 335 | 334 | | |
| Units: percentage of HbA1c | | | | |
| least squares mean (standard error) | -0.43 (± 0.042) | -0.38 (± 0.042) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Change from Baseline in Hemoglobin A1c (HbA1c) |
| Comparison groups | Insulin Lispro (Humalog) v LY900014 |
| Number of subjects included in analysis | 669 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Parameter estimate | Least Square Mean Difference (LSMean) |
| Point estimate | 0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 0.16 |

Secondary: 1-hour Postprandial Glucose (PPG) Excursion during Mixed-Meal Tolerance Test (MMTT) Efficacy Estimand

| | |
|-----------------|---|
| End point title | 1-hour Postprandial Glucose (PPG) Excursion during Mixed-Meal Tolerance Test (MMTT) Efficacy Estimand |
|-----------------|---|

End point description:

1-hour PPG excursion during MMTT uses the analysis of covariance (ANCOVA) model with strata (pooled country, type of basal insulin, number of prandial doses at study entry, and HbA1c stratum) and treatment as fixed effects and baseline as a covariate. The efficacy estimand included participant data when baseline and at least one post-baseline measurement were available prior to permanent discontinuation of study drug.

APD: All randomized participants with baseline and at least one post-baseline 1-hour PPG excursion data. As pre-specified in the analysis plan, outcome measures will not be reported for the MEE arms/groups but only for the main global study arms/groups.

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

End point timeframe:

Week 26

| | | | | |
|---|--------------------------|----------------------|--|--|
| End point values | Insulin Lispro (Humalog) | LY900014 | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 307 | 304 | | |
| Units: milligrams per deciliter (mg/dL) | | | | |
| least squares mean (standard error) | 74.9 (± 3.60) | 63.1 (± 3.60) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | 1-hour Postprandial Glucose (PPG) Excursion |
| Comparison groups | Insulin Lispro (Humalog) v LY900014 |
| Number of subjects included in analysis | 611 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -11.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18.1 |
| upper limit | -5.5 |

Secondary: 2-hour PPG Excursion during MMTT Efficacy Estimand

| | |
|---|--|
| End point title | 2-hour PPG Excursion during MMTT Efficacy Estimand |
| End point description: | 2-hour PPG excursion during MMTT uses the ANCOVA model with strata (pooled country, type of basal insulin, number of prandial doses at study entry, and HbA1c stratum) and treatment as fixed effects and baseline as a covariate. The efficacy estimand included participant data when baseline and at least one post-baseline measurement were available prior to permanent discontinuation of study drug. |
| APD: All randomized participants with baseline and at least one post-baseline 2-hour PPG excursion data. As pre-specified in the analysis plan, outcome measures will not be reported for the MEE arms/groups but only for the main global study arms/groups. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 26 | |

| | | | | |
|-------------------------------------|--------------------------|----------------------|--|--|
| End point values | Insulin Lispro (Humalog) | LY900014 | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 306 | 305 | | |
| Units: mg/dL | | | | |
| least squares mean (standard error) | 97.8 (± 4.50) | 80.4 (± 4.50) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | 2-hour PPG Excursion during MMTT Efficacy Estimand |
| Comparison groups | Insulin Lispro (Humalog) v LY900014 |
| Number of subjects included in analysis | 611 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -17.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -25.3 |
| upper limit | -9.5 |

Secondary: Rate of Severe Hypoglycemia

| | |
|--|-----------------------------|
| End point title | Rate of Severe Hypoglycemia |
| End point description: | |
| Rate of severe hypoglycemia events per 100 years during a defined period was calculated by total number of severe hypoglycemia episodes within the period divided by the cumulative days on treatment from all participants within a treatment group *36525. Severe hypoglycemia is defined as an event requiring assistance of another person to administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the participant has an altered mental status and cannot assist in his or her own care, or may be semiconscious or unconscious, or experience com with or without seizures, and may require parenteral therapy. | |
| APD: All randomized participants with evaluable hypoglycemic data. As pre-specified in the analysis plan, outcome measures will not be reported for the MEE arms/groups but only for the main global study arms/groups. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline through Week 26 | |

| | | | | |
|---|--------------------------|----------------------|--|--|
| End point values | Insulin Lispro (Humalog) | LY900014 | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 337 | 336 | | |
| Units: Events per 100 participant years | | | | |
| number (not applicable) | 4.19 | 2.44 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Documented Symptomatic Hypoglycemia

| | |
|-----------------|---|
| End point title | Rate of Documented Symptomatic Hypoglycemia |
|-----------------|---|

End point description:

Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by blood glucose (BG) of <54 mg/dL [3.0 millimole per liter (mmol/L)]. The rate of documented symptomatic hypoglycemia was estimated by negative binomial model: number of episodes = treatment with log (treatment exposure in days/365.25) as an offset variable.

APD: All randomized participants with evaluable hypoglycemic data. As pre-specified in the analysis plan, outcome measures will not be reported for the MEE arms/groups but only for the main global study arms/groups.

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

End point timeframe:

Baseline through Week 26

| End point values | Insulin Lispro (Humalog) | LY900014 | | |
|--|--------------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 337 | 336 | | |
| Units: Events per participant per year | | | | |
| least squares mean (standard error) | 1.34 (± 0.164) | 2.21 (± 0.318) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 1,5-Anhydroglucitol (1,5-AG) at Week 26

| | |
|-----------------|---|
| End point title | Change From Baseline in 1,5-Anhydroglucitol (1,5-AG) at Week 26 |
|-----------------|---|

End point description:

Change From baseline in 1,5-AG LSMean was calculated using Mixed Model Repeated Measures (MMRM) model including fixed class effects of treatment, strata (pooled country, type of basal insulin, HbA1c stratum and number of prandial doses at study entry), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline value. The analysis included data collected prior to permanent discontinuation of study drug.

APD: All randomized participants with baseline and at least one post-baseline 1,5-AG data. As pre-specified in the analysis plan, outcome measures will not be reported for the MEE arms/groups but only for the main global study arms/groups.

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

End point timeframe:

Baseline, Week 26

| End point values | Insulin Lispro (Humalog) | LY900014 | | |
|-------------------------------------|--------------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 334 | 331 | | |
| Units: milligram per liter (mg/L) | | | | |
| least squares mean (standard error) | 2.15 (\pm 0.234) | 1.99 (\pm 0.235) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in 10-Point Self-Monitoring Blood Glucose (SMBG) Values at Week 26

| | |
|-----------------|---|
| End point title | Change from Baseline in 10-Point Self-Monitoring Blood Glucose (SMBG) Values at Week 26 |
|-----------------|---|

End point description:

Change from baseline in 10-point SMBG values was calculated using MMRM model including fixed class effects of treatment, strata (pooled country, type of basal insulin, and number of prandial doses at study entry), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline value. The efficacy estimand included participant data when baseline and at least one post-baseline measurement prior to permanent discontinuation of study drug.

APD: All randomized participants with baseline and at least one post-baseline SMBG data. As pre-specified in the analysis plan, outcome measures will not be reported for the MEE arms/groups but only for the main global study arms/groups.

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

End point timeframe:

Baseline, Week 26

| End point values | Insulin Lispro (Humalog) | LY900014 | | |
|-------------------------------------|--------------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 276 | 270 | | |
| Units: mg/dL | | | | |
| least squares mean (standard error) | | | | |
| Morning Premeal | -0.8 (\pm 2.72) | 1.5 (\pm 2.74) | | |
| Morning 1-hour Postmeal | -2.0 (\pm 3.44) | -14.1 (\pm 3.44) | | |
| Morning 2-hour Postmeal | 0.6 (\pm 3.38) | -14.9 (\pm 3.38) | | |
| Midday Premeal | 2.4 (\pm 2.83) | 4.1 (\pm 2.84) | | |
| Midday 1-hour Postmeal | 3.0 (\pm 3.48) | -2.0 (\pm 3.47) | | |
| Midday 2-hour Postmeal | -2.2 (\pm 3.28) | -6.5 (\pm 3.27) | | |
| Evening Premeal | 7.0 (\pm 3.38) | 10.1 (\pm 3.38) | | |
| Evening 1-hour Postmeal | -2.1 (\pm 3.24) | -3.0 (\pm 3.27) | | |

| | | | | |
|------------------------------------|-------------------------------|--------------------------------|--|--|
| Evening 2-hour Postmeal Bedtime | 0.2 (± 3.68) -3.4 (± 4.00) | -2.1 (± 3.73) -2.2 (± 4.02) | | |
|------------------------------------|-------------------------------|--------------------------------|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Insulin Dose at Week 26

| | |
|-----------------|---|
| End point title | Change from Baseline in Insulin Dose at Week 26 |
|-----------------|---|

End point description:

Change from baseline in insulin dose was analyzed using mixed model repeated measure (MMRM) including fixed class effects of treatment, strata (pooled country, type of basal insulin, HbA1c stratum and number of prandial doses at study entry), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline value. The analysis included data prior to permanent discontinuation (d/c) of study drug (IP).

APD: All randomized participants with baseline and at least one post-baseline basal insulin dose data. As pre-specified in the analysis plan, outcome measures will not be reported for the MEE arms/groups but only for the main global study arms/groups.

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

End point timeframe:

Baseline, Week 26

| End point values | Insulin Lispro (Humalog) | LY900014 | | |
|---------------------------------------|-----------------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 330 | 330 | | |
| Units: Units (U) | | | | |
| least squares mean (standard error) | | | | |
| Basal Insulin Dose (n=317, 323) | 4.2 (± 0.82) | 4.6 (± 0.81) | | |
| Prandial Insulin Dose (n=330, 330) | 8.3 (± 1.41) | 12.0 (± 1.41) | | |
| Total Daily Insulin Dose (n=316, 321) | 12.1 (± 1.93) | 17.3 (± 1.92) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Insulin Treatment Satisfaction Questionnaire (ITSQ) Regimen Inconvenience Domain Score at Week 26

| | |
|-----------------|---|
| End point title | Change from Baseline in Insulin Treatment Satisfaction Questionnaire (ITSQ) Regimen Inconvenience Domain Score at Week 26 |
|-----------------|---|

End point description:

ITSQ is a validated instrument containing 22 items that assess treatment satisfaction for participants with diabetes and on insulin. The questionnaire measures satisfaction from the following 5 domains: Inconvenience of Regimen, Lifestyle Flexibility, Glycemic Control, Hypoglycemic Control, and Insulin Delivery Device. Data presented are the transformed overall score on a scale of 0-100, where higher

scores indicate better treatment satisfaction. Change from baseline in ITSQ regimen inconvenience domain score was calculated using the ANCOVA model with strata (pooled country, type of basal insulin, number of prandial doses at study entry, and HbA1c stratum), and treatment as fixed effects and baseline as covariate. Analysis includes data collected prior to d/c of IP.

APD: All randomized participants with baseline and post-baseline data. As pre-specified in the analysis plan, outcome measures will not be reported for the MEE arms/groups but only for the main global study arms/groups.

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

| | | | | |
|-------------------------------------|--------------------------|----------------------|--|--|
| End point values | Insulin Lispro (Humalog) | LY900014 | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 319 ^[1] | 319 ^[2] | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -0.9 (± 1.36) | -2.4 (± 1.37) | | |

Notes:

[1] - Missing endpoints were imputed by applying the LOCF method to post-baseline data.

[2] - Missing endpoints were imputed by applying the LOCF method to post-baseline data.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ITSQ Lifestyle Flexibility Domain Score at Week 26

| | |
|-----------------|--|
| End point title | Change from Baseline in ITSQ Lifestyle Flexibility Domain Score at Week 26 |
|-----------------|--|

End point description:

ITSQ is a validated instrument containing 22 items that assess treatment satisfaction for participants with diabetes and on insulin. The questionnaire measures satisfaction from the following 5 domains: Inconvenience of Regimen, Lifestyle Flexibility, Glycemic Control, Hypoglycemic Control, and Insulin Delivery Device. Data presented are the transformed overall score on a scale of 0-100, where higher scores indicate better treatment satisfaction. Change from baseline in ITSQ lifestyle flexibility domain score was calculated using the ANCOVA model with strata (pooled country, type of basal insulin, number of prandial doses at study entry, and HbA1c stratum), and treatment as fixed effects and baseline as covariate. Analysis includes data collected prior to d/c of IP.

APD: All randomized participants with baseline and post-baseline data. As pre-specified in the analysis plan, outcome measures will not be reported for the MEE arms/groups but only for the main global study arms/groups.

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

| | | | | |
|-------------------------------------|--------------------------|----------------------|--|--|
| End point values | Insulin Lispro (Humalog) | LY900014 | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 319 ^[3] | 319 ^[4] | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 1.4 (± 1.60) | 0.2 (± 1.60) | | |

Notes:

[3] - Missing endpoints were imputed by applying the LOCF method to the post-baseline data.

[4] - Missing endpoints were imputed by applying the LOCF method to the post-baseline data.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with HbA1c <7%

| | |
|-----------------|---------------------------------------|
| End point title | Number of Participants with HbA1c <7% |
|-----------------|---------------------------------------|

End point description:

Number of participants with HbA1c <7% at Week 26.

APD: All participants with baseline and 1 post-baseline observation while on study drug. As pre-specified in the analysis plan, outcome measures will not be reported for the MEE arms/groups but only for the main global study arms/groups.

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

End point timeframe:

Week 26

| | | | | |
|------------------------------|--------------------------|----------------------|--|--|
| End point values | Insulin Lispro (Humalog) | LY900014 | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 320 | 316 | | |
| Units: Count of participants | | | | |
| number (not applicable) | 168 | 184 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 weeks

Adverse event reporting additional description:

I8B-MC-ITRN

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | Insulin Lispro (Humalog) Lead-in |
|-----------------------|----------------------------------|

Reporting group description: -

| | |
|-----------------------|--------------------------|
| Reporting group title | Insulin Lispro (Humalog) |
|-----------------------|--------------------------|

Reporting group description: -

| | |
|-----------------------|----------|
| Reporting group title | LY900014 |
|-----------------------|----------|

Reporting group description: -

| | |
|-----------------------|--|
| Reporting group title | Insulin Lispro (Humalog) Lead-in Maximum Extended Enrollment |
|-----------------------|--|

Reporting group description: -

| | |
|-----------------------|--|
| Reporting group title | Insulin Lispro (Humalog) Maximum Extended Enrollment |
|-----------------------|--|

Reporting group description: -

| | |
|-----------------------|---|
| Reporting group title | LY900014 Maximum Extended Enrollment Cohort |
|-----------------------|---|

Reporting group description: -

| Serious adverse events | Insulin Lispro (Humalog) Lead-in | Insulin Lispro (Humalog) | LY900014 |
|---|----------------------------------|--------------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 13 / 750 (1.73%) | 26 / 337 (7.72%) | 26 / 336 (7.74%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| clear cell renal cell carcinoma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (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 |
| meningioma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (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 |
| renal neoplasm | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| hypertension | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| intermittent claudication | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 750 (0.13%) | 1 / 337 (0.30%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| peripheral arterial occlusive disease | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| peripheral artery stenosis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| peripheral vascular disorder | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| General disorders and administration site conditions | | | |
| non-cardiac chest pain | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| sudden death | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Immune system disorders | | | |
| drug hypersensitivity | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 750 (0.13%) | 0 / 337 (0.00%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| acute pulmonary oedema | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (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 |
| acute respiratory failure | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 2 / 336 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| bronchitis chronic | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| chronic obstructive pulmonary disease | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 3 / 336 (0.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| dyspnoea | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 2 / 336 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| laryngeal disorder | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 750 (0.13%) | 0 / 337 (0.00%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| blood potassium decreased | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| concussion | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 750 (0.13%) | 0 / 337 (0.00%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| fall | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 750 (0.13%) | 1 / 337 (0.30%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| heat stroke | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ligament sprain | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| multiple fractures | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (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 |
| spinal compression fracture | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| acute myocardial infarction | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| angina pectoris | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| angina unstable | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (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 |
| atrial fibrillation | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| cardiac failure | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (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 |
| coronary artery stenosis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 2 / 337 (0.59%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| myocardial infarction | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 750 (0.13%) | 0 / 337 (0.00%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| carpal tunnel syndrome | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| hypoglycaemic coma alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 750 (0.13%) | 0 / 337 (0.00%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| lumbar radiculopathy alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| syncope alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| transient ischaemic attack alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (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 |
| Ear and labyrinth disorders vertigo alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (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 |
| Eye disorders cataract alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 750 (0.13%) | 1 / 337 (0.30%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| eye haemorrhage | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (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 |
| papilloedema | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 750 (0.13%) | 0 / 337 (0.00%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| gastritis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| gastrointestinal haemorrhage | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (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 |
| pancreatitis acute | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| bile duct stone | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 750 (0.13%) | 0 / 337 (0.00%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| cholelithiasis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| diabetic ulcer | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| acute kidney injury | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| nephrolithiasis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ureteric compression | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| back pain | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (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 |
| intervertebral disc protrusion alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| lumbar spinal stenosis alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| osteoarthritis alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| cellulitis alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| empyema alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| eye infection viral alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (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 |
| gastroenteritis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| osteomyelitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| pneumonia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 750 (0.13%) | 0 / 337 (0.00%) | 4 / 336 (1.19%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| pyelonephritis acute | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (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 |
| septic shock | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 1 / 336 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| sinusitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 750 (0.00%) | 0 / 337 (0.00%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| urinary tract infection alternative dictionary used: MedDRA 21.1 subjects affected / exposed | 1 / 750 (0.13%) | 0 / 337 (0.00%) | 0 / 336 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders hypoglycaemia alternative dictionary used: MedDRA 21.1 subjects affected / exposed | 2 / 750 (0.27%) | 5 / 337 (1.48%) | 3 / 336 (0.89%) |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 6 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| shock hypoglycaemic alternative dictionary used: MedDRA 21.1 subjects affected / exposed | 0 / 750 (0.00%) | 1 / 337 (0.30%) | 0 / 336 (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 |

| Serious adverse events | Insulin Lispro (Humalog) Lead-in Maximum Extended Enrollment | Insulin Lispro (Humalog) Maximum Extended Enrollment | LY900014 Maximum Extended Enrollment Cohort |
|---|---|--|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | 4 / 82 (4.88%) | 2 / 82 (2.44%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) clear cell renal cell carcinoma alternative dictionary used: MedDRA 21.1 subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| meningioma alternative dictionary used: MedDRA 21.1 subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|----------------|
| renal neoplasm alternative dictionary used: MedDRA 21.1 subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders hypertension alternative dictionary used: MedDRA 21.1 subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| intermittent claudication alternative dictionary used: MedDRA 21.1 subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| peripheral arterial occlusive disease alternative dictionary used: MedDRA 21.1 subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| peripheral artery stenosis alternative dictionary used: MedDRA 21.1 subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| peripheral vascular disorder alternative dictionary used: MedDRA 21.1 subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions non-cardiac chest pain | | | |

| | | | |
|--|-----------------|----------------|----------------|
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| sudden death | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| drug hypersensitivity | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| acute pulmonary oedema | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| acute respiratory failure | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| bronchitis chronic | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| chronic obstructive pulmonary disease | | | |
| alternative dictionary used: | | | |

| | | | |
|---|-----------------|----------------|----------------|
| MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| dyspnoea | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| laryngeal disorder | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| blood potassium decreased | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| concussion | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| fall | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| heat stroke | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ligament sprain alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| multiple fractures alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| spinal compression fracture alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| acute myocardial infarction alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 82 (1.22%) | 0 / 82 (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 |
| angina pectoris alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| angina unstable alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| atrial fibrillation | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| cardiac failure | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| coronary artery stenosis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| myocardial infarction | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| carpal tunnel syndrome | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 82 (1.22%) | 0 / 82 (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 |
| hypoglycaemic coma | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| lumbar radiculopathy | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 82 (1.22%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| syncope | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 82 (1.22%) | 0 / 82 (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 |
| transient ischaemic attack | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| vertigo | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| cataract | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| eye haemorrhage | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| papilloedema | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| gastritis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| gastrointestinal haemorrhage | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| pancreatitis acute | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| bile duct stone | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| cholelithiasis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| diabetic ulcer | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| acute kidney injury | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| nephrolithiasis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ureteric compression | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| back pain | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| intervertebral disc protrusion | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| lumbar spinal stenosis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| osteoarthritis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| cellulitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| empyema | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| eye infection viral | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| gastroenteritis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| osteomyelitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| pneumonia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| pyelonephritis acute | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| septic shock | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| sinusitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 82 (1.22%) | 0 / 82 (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 |
| urinary tract infection | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|----------------|----------------|
| Metabolism and nutrition disorders | | | |
| hypoglycaemia | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| shock hypoglycaemic | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Insulin Lispro (Humalog) Lead-in | Insulin Lispro (Humalog) | LY900014 |
|--|-------------------------------------|-----------------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 44 / 750 (5.87%) | 60 / 337 (17.80%) | 79 / 336 (23.51%) |
| Gastrointestinal disorders | | | |
| diarrhoea | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 11 / 750 (1.47%) | 10 / 337 (2.97%) | 11 / 336 (3.27%) |
| occurrences (all) | 11 | 10 | 12 |
| Infections and infestations | | | |
| nasopharyngitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 23 / 750 (3.07%) | 38 / 337 (11.28%) | 47 / 336 (13.99%) |
| occurrences (all) | 25 | 47 | 56 |
| upper respiratory tract infection | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 13 / 750 (1.73%) | 20 / 337 (5.93%) | 27 / 336 (8.04%) |
| occurrences (all) | 13 | 21 | 29 |

| Non-serious adverse events | Insulin Lispro (Humalog) Lead-in Maximum Extended Enrollment | Insulin Lispro (Humalog) Maximum Extended Enrollment | LY900014 Maximum Extended Enrollment Cohort |
|--|---|--|---|
| Total subjects affected by non-serious adverse events | | | |

| subjects affected / exposed | 12 / 183 (6.56%) | 8 / 82 (9.76%) | 5 / 82 (6.10%) |
|---|------------------|----------------|----------------|
| Gastrointestinal disorders | | | |
| diarrhoea | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 5 / 82 (6.10%) | 0 / 82 (0.00%) |
| occurrences (all) | 2 | 5 | 0 |
| Infections and infestations | | | |
| nasopharyngitis | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 7 / 183 (3.83%) | 4 / 82 (4.88%) | 5 / 82 (6.10%) |
| occurrences (all) | 7 | 4 | 5 |
| upper respiratory tract infection | | | |
| alternative dictionary used: MedDRA 21.1 | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | 0 / 82 (0.00%) | 0 / 82 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|---|
| 19 May 2017 | - Immunogenicity follow-up shortened. - Primary analysis modified. |

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.

| |
|--|
| As pre-specified in the analysis plan, outcome measures will not be reported for the Maximum Extended Enrollment (MEE) arms/groups but only for the main global study arms/groups. |
|--|

Notes: