



Clinical trial results:

A Phase III, Multicenter, Observer-blind, Safety and Immunogenicity Study of Rabies Vaccine and Japanese Encephalitis Vaccine Administered Concomitantly and/or Separately According to 1 of 2 Different Pre-exposure Prophylaxis Schedules to Healthy Adult Subjects

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2011-005173-23 |
| Trial protocol | AT |
| Global end of trial date | 28 October 2013 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 11 June 2016 |
| First version publication date | 28 December 2014 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set re-QC of the study needed because of EudraCT system glitch and updates are required. |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | V49_23 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01662440 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Vaccines and Diagnostics SRL |
| Sponsor organisation address | Via Fiorentina 1 , Siena, Italy, 53100 |
| Public contact | Posting Director, Novartis Vaccines and Diagnostics SRL, RegistryContactVaccinesUS@novartis.com |
| Scientific contact | Posting Director , Novartis Vaccines and Diagnostics SRL, RegistryContactVaccinesUS@novartis.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 03 September 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 October 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of Rabies and JE vaccines given concomitantly or alone and according to either of 2 schedules for pre-exposure prophylaxis

Immunogenicity:

Primary:

1. To establish non-inferiority of the immune response of Rabies vaccine (administered concomitantly with JE vaccine) accelerated schedule as compared to Rabies vaccine administered alone following the conventional schedule.
2. To establish non-inferiority of the immune response of JE vaccine (administered concomitantly with Rabies vaccine), accelerated schedule as compared to JE vaccine administered alone following the conventional schedule.

Protection of trial subjects:

This trial was performed with the ethical principles that have their origin in the Declaration of Helsinki that are consistent with GCP according to International Conference on Harmonization (ICH) guidelines, the applicable regulatory requirements(s) for the country in which the study is conducted, and applicable standard operating procedures (SOPs). Specifically, this trial was based on adequately performed laboratory and animal experimentation; it was conducted under a protocol reviewed and approved by the EC and by scientifically and medically qualified persons; the benefits of the study were in proportion to the risks; the rights and welfare of the subjects were respected; the physicians conducting the trial did not find the hazards to outweigh the potential benefits; each subject, or where applicable, each subject's legally acceptable representative(s) gave his or her written informed consent before any protocol-driven tests or evaluations were performed. A copy of the ICH GCP guidelines and the Declaration of Helsinki were included in the investigator's study file.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------------------|
| Actual start date of recruitment | 06 August 2012 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Scientific research |
| Long term follow-up duration | 10 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Austria: 100 |
| Country: Number of subjects enrolled | Germany: 479 |
| Country: Number of subjects enrolled | Switzerland: 82 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 661 |
| EEA total number of subjects | 579 |

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) | 654 |
| From 65 to 84 years | 7 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from five sites in Germany, one site in Austria, and one site in Switzerland.

Pre-assignment

Screening details:

All subjects were included in the trial.

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, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Subjects were not informed which injections were active and which were placebo. All vaccines were assembled away from the view of the subject and blinded site staff members. All injections were administered by a designated unblinded staff member who was not involved in the evaluation of safety or in immunogenicity analyses. All other site personnel remained blinded to study vaccine group. Laboratory personnel determining antibody titers were not aware of vaccine group assignments.

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | R/JE – Conv |

Arm description:

Subjects received Rabies (R) and Japanese Encephalitis (JE) vaccines, conventional schedule, ie, Rabies vaccination on days 1, 8, and 29, and placebo on day 4 in the right arm or leg; and JE vaccination on day 1 and 29, and placebo on day 8 in the left arm.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Rabies, whole virus vaccine (inactivated, Germany) |
| Investigational medicinal product code | SUB25746 |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Subjects received three injections (days 1, 8, and 29) of 1 mL.

| | |
|--|---|
| Investigational medicinal product name | Japanese encephalitis vaccine (inactivated, adsorbed) |
| Investigational medicinal product code | SUB30399 |
| Other name | |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Subjects received two injections (days 1 and 29) of 0.5 mL.

| | |
|-----------|------------|
| Arm title | R/JE – Acc |
|-----------|------------|

Arm description:

Subjects received Rabies and JE vaccines, accelerated schedule, ie, Rabies vaccination on days 1, 4, and 8, and placebo on day 29 in the right arm or leg; and JE vaccination on days 1 and 8, and placebo on day 29 in the left arm.

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

| | |
|--|--|
| Investigational medicinal product name | Rabies, whole virus vaccine (inactivated, Germany) |
| Investigational medicinal product code | SUB25746 |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Subjects received three injections (days 1, 4, and 8) of 1 mL containing ≥ 2.5 IU of antigen.

| | |
|--|---|
| Investigational medicinal product name | Japanese encephalitis vaccine (inactivated, adsorbed) |
| Investigational medicinal product code | SUB30399 |
| Other name | |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Subjects received two injections (days 1 and 8) of 0.5 mL containing 6 μ g of antigen.

| | |
|------------------|----------|
| Arm title | R – Conv |
|------------------|----------|

Arm description:

Subjects received Rabies vaccine, conventional schedule, ie, Rabies vaccination on days 1, 8, and 29, and placebo on day 4 in the right arm or leg; and placebo on days 1, 8 and 29 in the left arm.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Rabies, whole virus vaccine (inactivated, Germany) |
| Investigational medicinal product code | SUB25746 |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Subjects received three injections (days 1, 8, and 29) of 1 mL.

| | |
|------------------|-----------|
| Arm title | JE – Conv |
|------------------|-----------|

Arm description:

Subjects received JE vaccine, conventional schedule, ie, placebo on days 1, 4, 8 and 29 in the right arm or leg; and JE vaccination on days 1 and 29 and placebo injection on day 8 in the left arm.

| | |
|--|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Japanese encephalitis vaccine (inactivated, adsorbed) |
| Investigational medicinal product code | SUB30399 |
| Other name | |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Subjects received two injections (days 1 and 29) of 0.5 mL.

| Number of subjects in period 1 | R/JE – Conv | R/JE – Acc | R – Conv |
|---------------------------------------|-------------|------------|----------|
| Started | 167 | 217 | 221 |
| Completed | 158 | 211 | 215 |
| Not completed | 9 | 6 | 6 |
| Consent withdrawn by subject | 5 | 2 | 2 |
| Adverse event, non-fatal | 1 | - | - |

| | | | |
|----------------------------------|---|---|---|
| Subject moved to another country | - | 1 | - |
| Death | - | 1 | - |
| Lost to follow-up | 2 | 2 | 4 |
| Protocol deviation | 1 | - | - |

| Number of subjects in period 1 | JE – Conv |
|---------------------------------------|-----------|
| Started | 56 |
| Completed | 52 |
| Not completed | 4 |
| Consent withdrawn by subject | 2 |
| Adverse event, non-fatal | 1 |
| Subject moved to another country | - |
| Death | - |
| Lost to follow-up | 1 |
| Protocol deviation | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | R/JE – Conv |
|-----------------------|-------------|

Reporting group description:

Subjects received Rabies (R) and Japanese Encephalitis (JE) vaccines, conventional schedule, ie, Rabies vaccination on days 1, 8, and 29, and placebo on day 4 in the right arm or leg; and JE vaccination on day 1 and 29, and placebo on day 8 in the left arm.

| | |
|-----------------------|------------|
| Reporting group title | R/JE – Acc |
|-----------------------|------------|

Reporting group description:

Subjects received Rabies and JE vaccines, accelerated schedule, ie, Rabies vaccination on days 1, 4, and 8, and placebo on day 29 in the right arm or leg; and JE vaccination on days 1 and 8, and placebo on day 29 in the left arm.

| | |
|-----------------------|----------|
| Reporting group title | R – Conv |
|-----------------------|----------|

Reporting group description:

Subjects received Rabies vaccine, conventional schedule, ie, Rabies vaccination on days 1, 8, and 29, and placebo on day 4 in the right arm or leg; and placebo on days 1, 8 and 29 in the left arm.

| | |
|-----------------------|-----------|
| Reporting group title | JE – Conv |
|-----------------------|-----------|

Reporting group description:

Subjects received JE vaccine, conventional schedule, ie, placebo on days 1, 4, 8 and 29 in the right arm or leg; and JE vaccination on days 1 and 29 and placebo injection on day 8 in the left arm.

| Reporting group values | R/JE – Conv | R/JE – Acc | R – Conv |
|------------------------|-------------|------------|----------|
| Number of subjects | 167 | 217 | 221 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|--------|--------|--------|
| Age continuous | | | |
| Analysis was done on the All Enrolled Set, ie, all subjects who have signed an informed consent, undergone screening procedure(s) and were randomized. | | | |
| Units: years | | | |
| arithmetic mean | 37.3 | 36.8 | 35.7 |
| standard deviation | ± 13.4 | ± 12.7 | ± 12.6 |
| Gender categorical | | | |
| Analysis was done on the all enrolled set, ie, all subjects who have signed an informed consent, undergone screening procedure(s) and were randomized. | | | |
| Units: Subjects | | | |
| Female | 76 | 128 | 125 |
| Male | 91 | 89 | 96 |

| Reporting group values | JE – Conv | Total | |
|------------------------|-----------|-------|--|
| Number of subjects | 56 | 661 | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|--|--|--|
| Age continuous | | | |
| Analysis was done on the All Enrolled Set, ie, all subjects who have signed an informed consent, undergone screening procedure(s) and were randomized. | | | |

| | | | |
|--|--------|-----|--|
| Units: years | | | |
| arithmetic mean | 38.8 | | |
| standard deviation | ± 13.3 | - | |
| Gender categorical | | | |
| Analysis was done on the all enrolled set, ie, all subjects who have signed an informed consent, undergone screening procedure(s) and were randomized. | | | |
| Units: Subjects | | | |
| Female | 30 | 359 | |
| Male | 26 | 302 | |

End points

End points reporting groups

| | |
|---|-------------|
| Reporting group title | R/JE – Conv |
| Reporting group description: Subjects received Rabies (R) and Japanese Encephalitis (JE) vaccines, conventional schedule, ie, Rabies vaccination on days 1, 8, and 29, and placebo on day 4 in the right arm or leg; and JE vaccination on day 1 and 29, and placebo on day 8 in the left arm. | |
| Reporting group title | R/JE – Acc |
| Reporting group description: Subjects received Rabies and JE vaccines, accelerated schedule, ie, Rabies vaccination on days 1, 4, and 8, and placebo on day 29 in the right arm or leg; and JE vaccination on days 1 and 8, and placebo on day 29 in the left arm. | |
| Reporting group title | R – Conv |
| Reporting group description: Subjects received Rabies vaccine, conventional schedule, ie, Rabies vaccination on days 1, 8, and 29, and placebo on day 4 in the right arm or leg; and placebo on days 1, 8 and 29 in the left arm. | |
| Reporting group title | JE – Conv |
| Reporting group description: Subjects received JE vaccine, conventional schedule, ie, placebo on days 1, 4, 8 and 29 in the right arm or leg; and JE vaccination on days 1 and 29 and placebo injection on day 8 in the left arm. | |

Primary: 1) Percentages of Subjects With RVNA Concentrations ≥ 0.5 IU/mL At 7 Days After Last Active Vaccination

| | |
|---|---|
| End point title | 1) Percentages of Subjects With RVNA Concentrations ≥ 0.5 IU/mL At 7 Days After Last Active Vaccination ^[1] |
| End point description: Immune response was measured as the percentage of subjects with rabies virus neutralizing antibody (RVNA) concentrations ≥ 0.5 IU/mL, evaluated using the rapid fluorescent focus inhibition test, before vaccination (day 1) and 7 days after last active vaccination, i.e. the third out of four vaccinations given in the accelerated Rabies vaccine schedule and the fourth out of four vaccinations given in the conventional Rabies vaccine schedule. As per study design, this primary immunogenicity outcome measure aimed to demonstrate non-inferiority of R/JE - Acc Vs R - Conv. Analysis was done on the per-protocol (PP) dataset, ie, the subjects who received the vaccine correctly, provided evaluable serum samples at the relevant time points, and had no major protocol violations as defined prior to unblinding. | |
| End point type | Primary |
| End point timeframe: Day 7 after last active vaccination (day 15 – group received accelerated schedule, day 36 – group received conventional schedule) | |

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: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Acc | R – Conv | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 207 | | |
| Units: Percentages of subjects | | | | |
| number (confidence interval 95%) | | | | |
| Day 7 after last active vaccination | 100 (97 to 100) | 100 (97 to 100) | | |

Statistical analyses

| Statistical analysis title | non-inferiority of the immune response |
|---|--|
| Statistical analysis description: | |
| To establish non-inferiority of the immune response of Rabies vaccine (administered concomitantly with JE vaccine) accelerated schedule as compared to Rabies vaccine administered alone following the conventional schedule at 7 days after last active vaccination. | |
| Comparison groups | R/JE – Acc v R – Conv |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[2] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Difference in percentages of subjects |
| Point estimate | 0 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -2.8 |
| upper limit | 2.8 |

Notes:

[2] - The immune response of accelerated schedule of the Rabies vaccine considered non-inferior to the conventional schedule if the lower bound of the two-sided 97.5% Confidence Intervals (CI) of the difference in the percentages of subjects with RVNA titer ≥ 0.5 IU/mL measured 7 days after last active vaccination is greater than -5.

Primary: 2) Percentages of Subjects With PRNT50 Titer $\geq 1:10$ At 28 Days After Last Active Vaccination

| | |
|---|--|
| End point title | 2) Percentages of Subjects With PRNT50 Titer $\geq 1:10$ At 28 Days After Last Active Vaccination ^[3] |
| End point description: | |
| Immune response was measured as the percentages of subjects with a titer of $\geq 1:10$ in a 50% plaque reduction neutralization test (PRNT50) 28 days after last active vaccination, ie, the second out of three vaccinations given in the accelerated JE vaccine schedule and the third out of three vaccinations given in the conventional JE vaccine schedule. As per study design, this primary immunogenicity outcome measure aimed to demonstrate non-inferiority of R/JE - Acc Vs JE - Conv. | |
| End point type | Primary |
| End point timeframe: | |
| Day 28 after last active vaccination (day 36 – group received accelerated schedule, day 57 – group received conventional schedule) | |

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Acc | JE – Conv | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 206 | 49 | | |
| Units: Percentages of subjects | | | | |
| number (confidence interval 95%) | | | | |
| Day 28 after last active vaccination | 99 (96 to 100) | 100 (93 to 100) | | |

Statistical analyses

| Statistical analysis title | Non-inferiority of the immune response |
|---|--|
| Statistical analysis description: | |
| Non-inferiority of the immune response of JE vaccine (administered concomitantly with Rabies vaccine) accelerated schedule as compared to JE vaccine administered alone following the conventional schedule at 28 day after last active vaccination | |
| Comparison groups | R/JE – Acc v JE – Conv |
| Number of subjects included in analysis | 255 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[4] |
| Method | Miettinen and Nurminen |
| Parameter estimate | Difference in percentages of subjects |
| Point estimate | -1 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -4.8 |
| upper limit | 7.9 |

Notes:

[4] - The immune response of accelerated schedule of the JE vaccine is considered non-inferior to the conventional schedule if the lower bound of the two-sided 97.5% CI of the difference in the percentages of subjects with PRNT50 titer $\geq 1:10$ measured 28 days after last active vaccination is greater than -10.

Secondary: 3) RVNA Geometric Mean Concentrations (GMCs) At 28Days After Last Active Vaccination

| End point title | 3) RVNA Geometric Mean Concentrations (GMCs) At 28Days After Last Active Vaccination ^[5] |
|--|---|
| End point description: | |
| Immune response was measured as the RVNA GMCs), 28 days after last active vaccination, i.e. day 57 for all groups that received the conventional schedule. Data were adjusted using ANOVA model, as per protocol specification. Analysis was done on the PP dataset. | |
| End point type | Secondary |
| End point timeframe: | |
| 28 days after last active vaccination (day 57) | |

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Conv | R – Conv | | |
|--|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 157 | 204 | | |
| Units: IU/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Day 28 after last active vaccination | 11 (9 to 12) | 9.9 (8.57 to 11) | | |

Statistical analyses

| Statistical analysis title | Non-inferiority of the immune response |
|--|--|
| Statistical analysis description: | |
| Non-inferiority of the immune response of Rabies vaccine (administered concomitantly with JE vaccine) as compared to Rabies vaccines (administered alone) as given according to conventional schedule at 28day after last active vaccination | |
| Comparison groups | R – Conv v R/JE – Conv |
| Number of subjects included in analysis | 361 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[6] |
| Parameter estimate | Between groups ratio of GMCs] |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 1.32 |

Notes:

[6] - The conventional schedule of Rabies vaccine co-administered with JE vaccine considered non inferior to the conventional schedule of Rabies vaccine administered alone if the lower bound of the two-sided 95% CI of the ratio of GMCs measured 28 days after last active vaccination is greater than 0.667.

Secondary: 4) PRNT50 GMTs At 28 Days After Last Active Vaccination

| End point title | 4) PRNT50 GMTs At 28 Days After Last Active Vaccination ^[7] |
|---|--|
| End point description: | |
| Immune response was measured as the PRNT50 GMTs 28 days after last active vaccination, ie, day 57 for all groups that received the conventional schedule. | |
| Data were adjusted using ANOVA model, as per protocol specifications. | |
| Analysis was done on the PP dataset. | |
| End point type | Secondary |
| End point timeframe: | |
| 28 days after last active vaccination (day 57) | |

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Conv | JE – Conv | | |
|--|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 157 | 49 | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Day 28 after last active vaccination | 291 (256 to 331) | 331 (265 to 415) | | |

Statistical analyses

| Statistical analysis title | Non-inferiority of the immune response |
|---|--|
| Statistical analysis description: | |
| Non-inferiority of the immune response of JE vaccine (administered concomitantly with Rabies vaccine) as compared to JE vaccine (administered alone) as given according to conventional schedule at day 28 after last active vaccination. | |
| Comparison groups | R/JE – Conv v JE – Conv |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[8] |
| Parameter estimate | Ratio of GMTs |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 1.13 |

Notes:

[8] - The conventional schedule of JE vaccine co-administered with Rabies vaccine considered non inferior to the conventional schedule of JE vaccine administered alone if the lower bound of the two-sided 95% CI of the ratio of GMTs measured 28 days after last active vaccination is greater than 0.5.

Secondary: 5) Percentages of Subjects With RVNA Concentrations ≥ 0.5 IU/mL At 28Days After Last Active Vaccination

| End point title | 5) Percentages of Subjects With RVNA Concentrations ≥ 0.5 IU/mL At 28Days After Last Active Vaccination ^[9] |
|---|---|
| End point description: | |
| Immune response was measured as the percentage of subjects with RVNA concentrations ≥ 0.5 IU/mL, 28 days after last active vaccination, i.e. day 36 for the group that received the accelerated schedule and day 57 for the group that received the conventional schedule. | |
| As per study design, this secondary immunogenicity outcome measure aimed to demonstrate non-inferiority of R/JE - Acc Vs R - Conv. | |
| Analysis was done on the PP set. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 36 and day 57 (28 days after last active vaccination) | |

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Acc | R – Conv | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 206 | 204 | | |
| Units: Percentages of subjects | | | | |
| number (confidence interval 95%) | | | | |
| Day 28 after last active vaccination | 99 (96 to 100) | 100 (97 to 100) | | |

Statistical analyses

| Statistical analysis title | Non-inferiority of the Rabies immune response |
|---|---|
| Statistical analysis description: | |
| Non-inferiority of the Rabies immune response (administered concomitantly with JE vaccine) as given according to an accelerated schedule as compared Rabies vaccine (administered alone) as given to a conventional schedule at day 28 after last active vaccination. | |
| Comparison groups | R/JE – Acc v R – Conv |
| Number of subjects included in analysis | 410 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[10] |
| Parameter estimate | Difference in percentages of subjects |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.8 |
| upper limit | 1.4 |

Notes:

[10] - The immune response of accelerated schedule of the Rabies vaccine is considered non-inferior to the Rabies vaccine conventional schedule if the lower bound of the two-sided 95% CI of the difference in the percentages of subjects with RVNA concentrations ≥ 0.5 IU/mL measured 28 days after last active vaccine administration is greater than -5.

Secondary: 6) Percentage of Subjects With PRNT50 Titer $\geq 1:10$ At 7 Days After Last Active Vaccination

| End point title | 6) Percentage of Subjects With PRNT50 Titer $\geq 1:10$ At 7 Days After Last Active Vaccination ^[11] |
|---|---|
| End point description: | |
| Immune response was measured as the percentage of subjects with PRNT50 titer of $\geq 1:10$, 7 days after last active vaccination, ie, day 15 for the group that received the accelerated schedule and day 36 for the group that received the conventional schedule. | |
| As per study design, this secondary immunogenicity outcome measure aimed to demonstrate non-inferiority of R/JE - Acc Vs JE - Conv. | |
| Analysis was done on the PP dataset. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 15 and day 36 (28 after last active vaccination) | |

Notes:

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

Justification: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Acc | JE – Conv | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 47 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| Day 7 after last active vaccination | 99 (96 to 100) | 100 (92 to 100) | | |

Statistical analyses

| Statistical analysis title | Non-inferiority of the immune response |
|--|--|
| Statistical analysis description: | |
| Non-inferiority of the immune response of JE vaccine (administered concomitantly with Rabies vaccine) as given according to an accelerated schedule as compared to JE vaccine (administered alone) as given according to a conventional schedule at 7day after last active vaccine administration. | |
| Comparison groups | R/JE – Acc v JE – Conv |
| Number of subjects included in analysis | 256 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[12] |
| Parameter estimate | Difference in percentages of subjects |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.1 |
| upper limit | 6.2 |

Notes:

[12] - The immune response of accelerated schedule of the JE vaccine considered non-inferior to the conventional schedule if the lower bound of the two-sided 95% CI of the difference in the percentages of subjects with PRNT50 titer $\geq 1:10$ measured 7 days after last active vaccine administration is greater than -10.

Secondary: 7) Kinetics of Rabies Immune Response Measured as Percentage of Subjects With RVNA Concentrations ≥ 0.5 IU/mL

| | |
|-----------------|--|
| End point title | 7) Kinetics of Rabies Immune Response Measured as Percentage of Subjects With RVNA Concentrations ≥ 0.5 IU/mL ^[13] |
|-----------------|--|

End point description:

To evaluate the kinetics of antibody response to Rabies vaccine, the immunogenicity was measured as the percentage of subjects with RVNA concentrations ≥ 0.5 IU/mL on days 1, 8, 15, 36, 57, 91, 181, and 366.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 1, 15, 36, 57, 91, 181 and Day 366 | |

Notes:

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

Justification: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Conv | R/JE – Acc | R – Conv | |
|----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 166 | 215 | 218 | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Day 1 | 1 (0.015 to 3) | 1 (0 to 3) | 1 (0 to 4) | |
| Day 8 (N=161, 210, 213) | 4 (2 to 9) | 16 (11 to 21) | 4 (2 to 8) | |
| Day 15 (N=161, 209, 210) | 99 (96 to 100) | 100 (97 to 100) | 99 (97 to 100) | |
| Day 36 (N=157, 206, 207) | 100 (98 to 100) | 99 (96 to 100) | 100 (97 to 100) | |
| Day 57 (157, 204, 204) | 100 (98 to 100) | 97 (93 to 99) | 100 (97 to 100) | |
| Day 91 (N=152, 206, 204) | 99 (95 to 100) | 85 (79 to 90) | 98 (95 to 99) | |
| Day 181 (N= 155, 200, 202) | 88 (82 to 92) | 75 (68 to 81) | 89 (84 to 93) | |
| Day 366 (154, 199, 204) | 76 (68 to 82) | 68 (61 to 74) | 80 (74 to 85) | |

Statistical analyses

No statistical analyses for this end point

Secondary: 8) Kinetics of Rabies Immune Response Measured as the RVNA GMCs

| | |
|-----------------|---|
| End point title | 8) Kinetics of Rabies Immune Response Measured as the RVNA GMCs ^[14] |
|-----------------|---|

End point description:

To evaluate the kinetics of antibody response to Rabies vaccine, the immunogenicity was measured as the RVNA GMCs on days 1, 8, 15, 36, 57, 91, 181, and 366.

Analysis was done on the PP dataset.

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

End point timeframe:

Day 1, 8, 15, 36, 57, 91, 181, and 366

Notes:

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

Justification: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Conv | R/JE – Acc | R – Conv | |
|--|------------------------|------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 166 | 215 | 218 | |
| Units: IU/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Day 1 | 0.052 (0.048 to 0.056) | 0.053 (0.049 to 0.056) | 0.054 (0.05 to 0.057) | |
| Day 8 (N=161, 210, 213) | 0.071 (0.061 to 0.084) | 0.13 (0.12 to 0.16) | 0.076 (0.066 to 0.088) | |
| Day 15 (N=161, 209, 210) | 21 (17 to 25) | 26 (22 to 30) | 24 (20 to 28) | |
| Day 36 (N=157, 206, 207) | 14 (12 to 17) | 5.75 (4.95 to 6.67) | 13 (11 to 15) | |
| Day 57 (N=157, 204, 204) | 10 (8.72 to 12) | 3.01 (2.59 to 3.51) | 9.66 (8.31 to 11) | |

| | | | | |
|----------------------------|---------------------|---------------------|---------------------|--|
| Day 91 (N=152, 206, 204) | 4.79 (3.98 to 5.76) | 1.63 (1.39 to 1.91) | 5.04 (4.29 to 5.91) | |
| Day 181 (N= 155, 200, 202) | 1.86 (1.51 to 2.3) | 1 (0.83 to 1.21) | 2.04 (1.69 to 2.46) | |
| Day 366 (N=154, 199, 204) | 0.93 (0.75 to 1.16) | 0.82 (0.67 to 1) | 1.14 (0.94 to 1.38) | |

Statistical analyses

No statistical analyses for this end point

Secondary: 9) Kinetics of JE Immune Response Measured as Percentages of Subjects With PRNT50 $\geq 1:10$ IU/mL

| | |
|-----------------|---|
| End point title | 9) Kinetics of JE Immune Response Measured as Percentages of Subjects With PRNT50 $\geq 1:10$ IU/mL ^[15] |
|-----------------|---|

End point description:

To evaluate the kinetics of antibody response to JE vaccine, the immunogenicity was measured as the percentages of subjects with PRNT50 titer $\geq 1:10$ on days 1, 36, 57, 181, and 366 (group that received JE vaccine as a conventional schedule).

Analysis was done on the PP dataset.

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

End point timeframe:

Days 1, 36, 57, 181 and 366

Notes:

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

Justification: There was no statistical analysis done for this endpoint.

| End point values | R/JE - Conv | JE - Conv | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 165 | 55 | | |
| Units: Percentages of subjects | | | | |
| number (confidence interval 95%) | | | | |
| Day 1 | 1 (0 to 4) | 9 (3 to 20) | | |
| Day 36 (157, 47) | 99 (97 to 100) | 100 (92 to 100) | | |
| Day 57 (N=157, 49) | 100 (98 to 100) | 100 (93 to 100) | | |
| Day 181 (N=155, 49) | 94 (88 to 97) | 92 (80 to 98) | | |
| Day 366 (N=154, 48) | 86 (79 to 91) | 88 (75 to 95) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 10) Kinetics of JE Immune Response Measured as Percentage of Subjects With PRNT50 Titers $\geq 1:10$

| | |
|-----------------|--|
| End point title | 10) Kinetics of JE Immune Response Measured as Percentage of Subjects With PRNT50 Titers $\geq 1:10$ ^[16] |
|-----------------|--|

End point description:

To evaluate the kinetics of antibody response to JE vaccine, the immunogenicity was measured as the percentage of subjects with PRNT50 titer $\geq 1:10$ on days 1, 15, 22, 36, 57, 91, 181, and 366 (group that received JE vaccine as an accelerated schedule).

Analysis was done on the PP dataset.

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

End point timeframe:

Day 1, 15, 22, 36, 57, 91, 181, and 366

Notes:

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

Justification: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Acc | | | |
|--|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 215 | | | |
| Units: Percentage of Subjects | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Day 1 | 6 (3 to 10) | | | |
| Day 15 (N= 209) | 99 (96 to 100) | | | |
| Day 22 (N= 208) | 100 (97 to 100) | | | |
| Day 36 (N= 206) | 99 (96 to 100) | | | |
| Day 57 (N= 204) | 98 (95 to 100) | | | |
| Day 91 (N= 206) | 98 (95 to 99) | | | |
| Day 181 (N= 200) | 98 (94 to 99) | | | |
| Day 366 (N= 199) | 94 (90 to 97) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 11) Kinetics of JE Immune Response Measured as PRNT50 GMTs

| | |
|-----------------|--|
| End point title | 11) Kinetics of JE Immune Response Measured as PRNT50 GMTs ^[17] |
|-----------------|--|

End point description:

To evaluate the kinetics of antibody response to JE vaccine, the immunogenicity was measured as the PRNT50 GMTs on days 1, 36, 57, 181, and 366 (groups that received JE vaccine as a conventional schedule).

Analysis was done on the PP dataset.

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

End point timeframe:

day 1, 36, 57, 181, and 366

Notes:

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

Justification: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Conv | JE – Conv | | |
|--|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 165 | 55 | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Day 1 | 5.13 (4.84 to 5.43) | 5.73 (5.2 to 6.33) | | |
| Day 36 (N=157, 47) | 292 (247 to 346) | 376 (277 to 510) | | |
| Day 57 (N= 157, 49) | 299 (254 to 352) | 337 (252 to 451) | | |
| Day 181 (N=155, 49) | 63 (53 to 75) | 64 (47 to 87) | | |
| Day 366 (N=154, 48) | 39 (33 to 47) | 39 (28 to 54) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 12) Kinetics of JE Immune Response Measured as PRNT50 GMTs

| | |
|-----------------|--|
| End point title | 12) Kinetics of JE Immune Response Measured as PRNT50 GMTs ^[18] |
|-----------------|--|

End point description:

To evaluate the kinetics of antibody response to JE vaccine, the immunogenicity was measured as the PRNT50 GMTs on days 1, 15, 22, 36, 57, 91, 181, and 366 (group that received JE vaccine as an accelerated schedule).

Analysis was done on the PP dataset.

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

End point timeframe:

Day 1, 15, 22, 36, 57, 91, 181, and 366

Notes:

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

Justification: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Acc | | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 215 | | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Day 1 | 5.63 (5.35 to 5.92) | | | |
| Day 15 (N= 209) | 715 (608 to 842) | | | |
| Day 22 (N= 208) | 1255 (1068 to 1475) | | | |
| Day 36 (N= 206) | 690 (595 to 801) | | | |
| Day 57 (N= 204) | 372 (322 to 430) | | | |
| Day 91 (N= 206) | 228 (192 to 272) | | | |

| | | | | |
|------------------|------------------|--|--|--|
| Day 181 (N= 200) | 151 (130 to 176) | | | |
| Day 366 (N= 199) | 117 (100 to 137) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 13) Number of Subjects Who Reported Solicited Local Adverse Events After Each Rabies Vaccination, conventional schedule

| | |
|-----------------|---|
| End point title | 13) Number of Subjects Who Reported Solicited Local Adverse Events After Each Rabies Vaccination, conventional schedule ^[19] |
|-----------------|---|

End point description:

Safety was assessed as the number of subjects who reported solicited local adverse events (AEs) after each rabies vaccination given according to the conventional schedule as follows: from day 1 through day 7 (vaccination on day 1), day 8 through day 14 (vaccination on day 8), or day 29 through day 35 (vaccination on day 29).

Analysis was done on the solicited safety set, i.e. the subjects in the exposed population who provided postvaccination solicited safety data.

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

End point timeframe:

Day 1 through day 7 after each vaccination (day 1, 8 and 29)

Notes:

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

Justification: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Conv | R – Conv | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 166 | 220 | | |
| Units: Number of Subjects | | | | |
| Erythema (day 1 to 7) | 13 | 28 | | |
| Induration (day 1 to 7) | 3 | 11 | | |
| Pain (day 1 to 7) | 43 | 72 | | |
| Erythema (day 8 to 14) | 8 | 29 | | |
| Induration (day 8 to 14) | 10 | 17 | | |
| Pain (day 8 to 14) | 57 | 90 | | |
| Erythema (day 29 to 35) | 23 | 45 | | |
| Induration (day 29 to 35) | 18 | 32 | | |
| Pain (day 29 to 35) | 52 | 87 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 14) Number of Subjects Who Reported Solicited Local Adverse Events After Each Rabies Vaccination, accelerated schedule

| | |
|-----------------|---|
| End point title | 14) Number of Subjects Who Reported Solicited Local Adverse |
|-----------------|---|

End point description:

Safety was assessed as the number of subjects who reported solicited local adverse events (AEs) after each rabies vaccination given according to accelerated schedule as follows: from day 1 through day 7 (vaccination on day 1), day 4 through day 10 (vaccination on day 4), day 8 through day 14 (vaccination on day 8).

Analysis was done on the solicited safety set.

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

End point timeframe:

Day 1 through day 7 after each vaccination (on day 1, 4, 8 and 29)

Notes:

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

Justification: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Acc | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 217 | | | |
| Units: Number of Subjects | | | | |
| Erythema (day 1 to 7) | 31 | | | |
| Induration (day 1 to 7) | 16 | | | |
| Pain (day 1 to 7) | 69 | | | |
| Erythema (day 4 to 10) | 17 | | | |
| Induration (day 4 to 10) | 9 | | | |
| Pain (day 4 to 10) | 55 | | | |
| Erythema (day 8 to 14) | 31 | | | |
| Induration (day 8 to 14) | 15 | | | |
| Pain (day 8 to 14) | 87 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 15) Number of Subjects Who Reported Solicited Local AEs After Each JE Vaccination, conventional schedule

| | |
|-----------------|--|
| End point title | 15) Number of Subjects Who Reported Solicited Local AEs After Each JE Vaccination, conventional schedule ^[21] |
|-----------------|--|

End point description:

Safety was assessed as the number of subjects who reported solicited local AEs after each JE vaccination given according to conventional schedule as follow: from day 1 through day 7 (vaccination on day 1) and day 29 through day 35 (vaccination on day 29).

Analysis was done on the solicited safety set.

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

End point timeframe:

Day 1 through day 7 after each vaccination (on day 1 and 29)

Notes:

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

Justification: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Conv | JE – Conv | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 166 | 56 | | |
| Units: Number of Subjects | | | | |
| Erythema (day 1 to 7) | 20 | 6 | | |
| Induration (day 1 to 7) | 13 | 5 | | |
| Pain (day 1 to 7) | 82 | 26 | | |
| Erythema (day 29 to 35) | 12 | 5 | | |
| Induration (day 29 to 35) | 5 | 4 | | |
| Pain (day 29 to 35) | 46 | 12 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 16) Number of Subjects Who Reported Solicited Local AEs After Each JE Vaccination, accelerated schedule

| | |
|-----------------|---|
| End point title | 16) Number of Subjects Who Reported Solicited Local AEs After Each JE Vaccination, accelerated schedule ^[22] |
|-----------------|---|

End point description:

Safety was assessed as the number of subjects who reported solicited local AEs after each JE vaccination given according to accelerated or conventional schedule as follow: from day 1 through day 7 (vaccination on day 1), day 8 through day 14 (vaccination on day 8).

Analysis was done on the solicited safety set.

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

End point timeframe:

Day 1 through day 7 after each vaccination (on day 1 and 8)

Notes:

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

Justification: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Acc | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 217 | | | |
| Units: Number of Subjects | | | | |
| Erythema (day 1 to 7) | 30 | | | |
| Induration (day 1 to 7) | 19 | | | |
| Pain (day 1 to 7) | 102 | | | |
| Erythema (day 8 to 14) | 18 | | | |
| Induration (day 8 to 14) | 12 | | | |
| Pain (day 8 to 14) | 60 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 17) Number of Subjects in the R/JE – Conv group Who Reported Solicited Local AEs After Each Placebo Injection

| | |
|-----------------|---|
| End point title | 17) Number of Subjects in the R/JE – Conv group Who Reported Solicited Local AEs After Each Placebo Injection ^[23] |
|-----------------|---|

End point description:

Safety was assessed as the number of subjects in the R/JE – Conv group who reported solicited local AEs after each placebo injection given according to conventional schedule as follow: from day 4 through day 10 (injection on day 4) and day 8 through day 14 (injection on day 8).
Analysis was done on the solicited safety set.

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

End point timeframe:

Day 1 through day 7 after each injection (day 4 and 8)

Notes:

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

Justification: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Conv | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 166 | | | |
| Units: Number of Subjects | | | | |
| Erythema (day 4 to 10) | 8 | | | |
| Induration (day 4 to 10) | 1 | | | |
| Pain (day 4 to 10) | 7 | | | |
| Erythema (day 8 to 14) | 1 | | | |
| Induration (day 8 to 14) | 0 | | | |
| Pain (day 8 to 14) | 19 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 18) Number of Subjects in the R/JE – Accelerated schedule group Who Reported Solicited Local AEs After Each Placebo Injection

| | |
|-----------------|---|
| End point title | 18) Number of Subjects in the R/JE – Accelerated schedule group Who Reported Solicited Local AEs After Each Placebo Injection ^[24] |
|-----------------|---|

End point description:

Safety was assessed as the number of subjects who reported solicited local AEs after each placebo injection given according to accelerated schedule as follow: from day 29 through day 35 (injection on day 29).
Analysis was done on the solicited safety set.

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

End point timeframe:

Day 1 through day 7 after each injection (day 1, 4, 8 and 29)

Notes:

[24] - 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: There was no statistical analysis done for this endpoint.

| End point values | R/JE – Acc | | | |
|--|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 213 | | | |
| Units: Number of Subjects | | | | |
| Erythema (day 29 to 35) | 15 | | | |
| Erythema (day 29 to 35 after 2nd Placebo dose) | 14 | | | |
| Induration (day 29 to 35) | 6 | | | |
| Induration (day 29 to 35 after 2nd Placebo dose) | 4 | | | |
| Pain (day 29 to 35) | 15 | | | |
| Pain (day 29 to 35 after 2nd Placebo dose) | 19 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 19) Number of Subjects in the R – Conventional schedule group Who Reported Solicited Local AEs After Each Placebo Injection

| | |
|-----------------|---|
| End point title | 19) Number of Subjects in the R – Conventional schedule group Who Reported Solicited Local AEs After Each Placebo Injection ^[25] |
|-----------------|---|

End point description:

Safety was assessed as the number of subjects in the R – Conventional schedule group who reported solicited local AEs after each placebo injection given according to conventional schedule as follow: from day 1 through day 7 (injection on day 1), day 4 through day 10 (injection on day 4), day 8 through day 14 (injection on day 8), and day 29 through day 35 (injection on day 29).

Analysis was done on the solicited safety set.

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

End point timeframe:

Day 1 through day 7 after each injection (day 1, 4, 8 and 29)

Notes:

[25] - 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: There was no statistical analysis done for this endpoint.

| End point values | R – Conv | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 220 | | | |
| Units: Number of Subjects | | | | |
| Erythema (day 1 to 7) | 20 | | | |
| Induration (day 1 to 7) | 4 | | | |
| Pain (day 1 to 7) | 26 | | | |
| Erythema (day 4 to 10) | 13 | | | |
| Induration (day 4 to 10) | 4 | | | |
| Pain (day 4 to 10) | 15 | | | |
| Erythema (day 8 to 14) | 11 | | | |
| Induration (day 8 to 14) | 5 | | | |
| Pain (day 8 to 14) | 20 | | | |
| Erythema (day 29 to 35) | 15 | | | |

| | | | | |
|---------------------------|----|--|--|--|
| Induration (day 29 to 35) | 4 | | | |
| Pain (day 29 to 35) | 28 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 20) Number of Subjects in the JE – Conventional schedule group Who Reported Solicited Local AEs After Each Placebo Injection

| | |
|-----------------|--|
| End point title | 20) Number of Subjects in the JE – Conventional schedule group Who Reported Solicited Local AEs After Each Placebo Injection ^[26] |
|-----------------|--|

End point description:

Safety was assessed as the number of subjects in the JE – Conventional schedule group who reported solicited local AEs after each placebo injection given according to conventional schedule as follow: from day 1 through day 7 (injection on day 1), day 4 through day 10 (injection on day 4), day 8 through day 14 (injection on day 8), and day 29 through day 35 (injection on day 29).

Analysis was done on the solicited safety set.

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

End point timeframe:

Day 1 through day 7 after each injection (day 1, 4, 8 and 29)

Notes:

[26] - 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: There was no statistical analysis done for this endpoint.

| End point values | JE – Conv | | | |
|---|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 56 | | | |
| Units: Number of Subjects | | | | |
| Erythema (day 1 to 7) | 3 | | | |
| Induration (day 1 to 7) | 5 | | | |
| Pain (day 1 to 7) | 7 | | | |
| Erythema (day 4 to 10) | 3 | | | |
| Induration (day 4 to 10) | 2 | | | |
| Pain (day 4 to 10) | 3 | | | |
| Erythema (day 8 to 14) | 4 | | | |
| Erythema (day 8 to 14 after 2nd Placebo dose) | 3 | | | |
| Induration (day 8 to 14) | 1 | | | |
| Induration (day 8 to 14 after 2nd Placebo dose) | 1 | | | |
| Pain (day 8 to 14) | 3 | | | |
| Pain (day 8 to 14 after 2nd Placebo dose) | 5 | | | |
| Erythema (day 29 to 35) | 3 | | | |
| Induration (day 29 to 35) | 1 | | | |
| Pain (day 29 to 35) | 3 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 21) Number of Subjects Who Reported Solicited Systemic AEs and Other Indicators of Reactogenicity After Each Vaccination

| | |
|-----------------|--|
| End point title | 21) Number of Subjects Who Reported Solicited Systemic AEs and Other Indicators of Reactogenicity After Each Vaccination |
|-----------------|--|

End point description:

Safety was assessed as the number of subjects who reported solicited systemic AEs and other indicators of reactogenicity after each vaccination given according to accelerated and conventional schedule. Analysis was done on the solicited safety set.

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

End point timeframe:

Day 1 through day 7 after each vaccination (day 1, 4, 8 and 29)

| End point values | R/JE – Conv | R/JE – Acc | R – Conv | JE – Conv |
|---|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 166 | 217 | 220 | 56 |
| Units: Number of Subjects | | | | |
| Fatigue (day 1 to 7) | 39 | 56 | 46 | 16 |
| Headache (day 1 to 7) | 35 | 46 | 38 | 14 |
| Myalgia (day 1 to 7) | 27 | 55 | 31 | 7 |
| Arthralgia (day 1 to 7) | 8 | 13 | 7 | 1 |
| Loss of Appetite (day1 to day 7) | 10 | 8 | 12 | 6 |
| Nausea (day1 to day 7) | 8 | 7 | 13 | 4 |
| Body temperature (≥ 38 °C, day 1 to day 7) | 1 | 2 | 2 | 0 |
| Analgesic/Antipyretic used (day 1 to day 7) | 11 | 11 | 8 | 3 |
| Fatigue (day 4 to 10) | 14 | 30 | 33 | 5 |
| Headache (day 4 to 10) | 17 | 28 | 29 | 3 |
| Myalgia (day 4 to 10) | 11 | 19 | 14 | 1 |
| Arthralgia (day 4 to 10) | 1 | 9 | 9 | 0 |
| Loss of Appetite (day4 to day 10) | 4 | 8 | 9 | 2 |
| Nausea (day4 to day 10) | 4 | 5 | 8 | 0 |
| Body temperature (≥ 38 °C, day 4 to day 10) | 1 | 1 | 2 | 0 |
| Analgesic/Antipyretic used (day 4 to 10) | 8 | 10 | 15 | 2 |
| Fatigue (day 8 to 14) | 24 | 47 | 47 | 6 |
| Headache (day 8 to 14) | 33 | 43 | 41 | 3 |
| Myalgia (day 8 to 14) | 22 | 41 | 38 | 1 |
| Arthralgia (day 8 to 14) | 6 | 9 | 13 | 1 |
| Loss of Appetite (day8 to day 14) | 10 | 14 | 13 | 2 |

| | | | | |
|--|----|----|----|---|
| Nausea (day8 to day 14) | 5 | 14 | 16 | 2 |
| Body temperature (≥ 38 °C, day 8 to 14) | 2 | 1 | 5 | 0 |
| Analgesic/Antipyretic used (day 8 to 14) | 10 | 17 | 20 | 2 |
| Fatigue (day 29 to 35) | 21 | 29 | 36 | 3 |
| Headache (day 29 to 35) | 27 | 22 | 40 | 4 |
| Myalgia (day 29 to 35) | 23 | 15 | 28 | 2 |
| Arthralgia (day 29 to 35) | 5 | 6 | 14 | 1 |
| Body temperature (≥ 38 °C, day 29 to day 35) | 1 | 2 | 1 | 0 |
| Analgesic/Antipyretic used (day 29 to day 35) | 9 | 10 | 11 | 3 |
| Loss if appetite (day 29 to day 25) | 2 | 8 | 9 | 2 |
| nausea (day29 to day 25) | 7 | 12 | 9 | 2 |

Statistical analyses

No statistical analyses for this end point

Secondary: 22) Numbers of Subjects Reporting Unsolicited AEs After Any Vaccination From Day 1 Through Day 57

| | |
|-----------------|---|
| End point title | 22) Numbers of Subjects Reporting Unsolicited AEs After Any Vaccination From Day 1 Through Day 57 |
|-----------------|---|

End point description:

Safety was assessed as the number of subjects who reported unsolicited AEs after any vaccination given according to accelerated and conventional schedule.

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

End point timeframe:

Day 1 through Day 57

| End point values | R/JE – Conv | R/JE – Acc | R – Conv | JE – Conv |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 166 | 217 | 220 | 56 |
| Units: Numbers of Subjects | | | | |
| Any AE | 69 | 108 | 110 | 29 |
| SAE | 2 | 3 | 2 | 3 |
| AEs leading to premature withdrawal | 1 | 0 | 0 | 1 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited AEs were collected for 7 days after each vaccination. All unsolicited AEs, serious adverse events (SAEs), AEs leading to study and/or treatment withdrawal were collected through day 57. From day 57 to day 366 vaccine-related SAEs were collected.

Adverse event reporting additional description:

Solicited adverse events were collected by systematic assessment, unsolicited AEs by non-systematic assessment. SAEs analysis was done on the unsolicited safety set, other AEs analysis was done on the overall safety set.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | R/JE – Conv |
|-----------------------|-------------|

Reporting group description:

Subjects received Rabies (R) and Japanese Encephalitis (JE) vaccines, conventional schedule, ie, Rabies vaccination on days 1, 8, and 29, and placebo on day 4 in the right arm or leg; and JE vaccination on day 1 and 29, and placebo on day 8 in the left arm.

| | |
|-----------------------|----------|
| Reporting group title | R – Conv |
|-----------------------|----------|

Reporting group description:

Subjects received Rabies vaccine, conventional schedule, ie, Rabies vaccination on days 1, 8, and 29, and placebo on day 4 in the right arm or leg; and placebo on days 1, 8 and 29 in the left arm.

| | |
|-----------------------|-----------|
| Reporting group title | JE – Conv |
|-----------------------|-----------|

Reporting group description:

Subjects received JE vaccine, conventional schedule, ie, placebo on days 1, 4, 8 and 29 in the right arm or leg; and JE vaccination on days 1 and 29 and placebo injection on day 8 in the left arm.

| | |
|-----------------------|------------|
| Reporting group title | R/JE – Acc |
|-----------------------|------------|

Reporting group description:

Subjects received Rabies and JE vaccines, accelerated schedule, ie, Rabies vaccination on days 1, 4, and 8, and placebo on day 29 in the right arm or leg; and JE vaccination on days 1 and 8, and placebo on day 29 in the left arm.

| Serious adverse events | R/JE – Conv | R – Conv | JE – Conv |
|---|-----------------|-----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 166 (1.20%) | 2 / 220 (0.91%) | 3 / 56 (5.36%) |
| 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) | | | |
| Ovarian germ cell teratoma benign | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 0 / 220 (0.00%) | 0 / 56 (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 | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 166 (0.60%) | 0 / 220 (0.00%) | 0 / 56 (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 |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 0 / 220 (0.00%) | 0 / 56 (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 | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 1 / 220 (0.45%) | 0 / 56 (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 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 1 / 220 (0.45%) | 0 / 56 (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 |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 1 / 220 (0.45%) | 0 / 56 (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 |
| Eye disorders | | | |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 0 / 220 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 0 / 220 (0.00%) | 0 / 56 (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 | | | |
| Cholecystitis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 166 (0.00%) | 0 / 220 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 0 / 220 (0.00%) | 1 / 56 (1.79%) |
| 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 | | | |
| Pruritus generalised | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 0 / 220 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Alcohol withdrawal syndrome | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 0 / 220 (0.00%) | 1 / 56 (1.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 1 / 166 (0.60%) | 0 / 220 (0.00%) | 0 / 56 (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 |

| Serious adverse events | R/JE – Acc | | |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 217 (1.38%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Ovarian germ cell teratoma benign | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 217 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Meniscus injury | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 217 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus generalised | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Alcohol withdrawal syndrome | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depression | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | R/JE – Conv | R – Conv | JE – Conv |
|---|--------------------|--------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 138 / 166 (83.13%) | 185 / 220 (84.09%) | 45 / 56 (80.36%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 63 / 166 (37.95%) | 95 / 220 (43.18%) | 19 / 56 (33.93%) |
| occurrences (all) | 139 | 189 | 30 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 54 / 166 (32.53%) | 84 / 220 (38.18%) | 19 / 56 (33.93%) |
| occurrences (all) | 107 | 189 | 33 |

| | | | |
|---|---------------------------|---------------------------|------------------------|
| Injection site erythema subjects affected / exposed occurrences (all) | 48 / 166 (28.92%) 90 | 85 / 220 (38.64%) 163 | 13 / 56 (23.21%) 28 |
| Injection site induration subjects affected / exposed occurrences (all) | 29 / 166 (17.47%) 54 | 48 / 220 (21.82%) 77 | 10 / 56 (17.86%) 19 |
| Injection site pain subjects affected / exposed occurrences (all) | 115 / 166 (69.28%) 314 | 131 / 220 (59.55%) 342 | 31 / 56 (55.36%) 62 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 19 / 166 (11.45%) 29 | 35 / 220 (15.91%) 52 | 9 / 56 (16.07%) 10 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 13 / 166 (7.83%) 21 | 31 / 220 (14.09%) 48 | 3 / 56 (5.36%) 3 |
| Myalgia subjects affected / exposed occurrences (all) | 50 / 166 (30.12%) 86 | 60 / 220 (27.27%) 115 | 10 / 56 (17.86%) 13 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 22 / 166 (13.25%) 25 | 32 / 220 (14.55%) 36 | 7 / 56 (12.50%) 7 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 19 / 166 (11.45%) 31 | 27 / 220 (12.27%) 50 | 9 / 56 (16.07%) 12 |

| | | | |
|--|--------------------------|--|--|
| Non-serious adverse events | R/JE – Acc | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 186 / 217 (85.71%) | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 94 / 217 (43.32%) 185 | | |
| General disorders and administration site conditions | | | |

| | | | |
|--|---|--|--|
| Fatigue subjects affected / exposed occurrences (all) | 93 / 217 (42.86%) 182 | | |
| Injection site erythema subjects affected / exposed occurrences (all) | 73 / 217 (33.64%) 160 | | |
| Injection site induration subjects affected / exposed occurrences (all) | 43 / 217 (19.82%) 81 | | |
| Injection site pain subjects affected / exposed occurrences (all) | 146 / 217 (67.28%) 418 | | |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 31 / 217 (14.29%) 44 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) | 29 / 217 (13.36%) 37 75 / 217 (34.56%) 137 | | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 33 / 217 (15.21%) 37 | | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 24 / 217 (11.06%) 43 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 06 April 2012 | Protocol Number V49_23, Version 2.0, Amendment 1 – Date: 06 APR 12, (revised from Version 1.0, Date: 05 DEC 11) |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported