



Clinical trial results:

Double-blind extension of the study 27025 (REFLEX) to obtain long-term follow-up data in patients with clinically definite MS and patients with a first demyelinating event at high risk of converting to MS, treated with Rebif® New Formulation (REFLEXION)

Summary

| | |
|--------------------------|--|
| EudraCT number | 2008-004954-34 |
| Trial protocol | CZ AT FI ES PT EE DE BE LV GR IT FR BG PL SK |
| Global end of trial date | 30 August 2013 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 15 April 2016 |
| First version publication date | 01 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | 28981 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00813709 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Merck KGaA |
| Sponsor organisation address | Frankfurter Strasse 250, Darmstadt, Germany, 64293 |
| Public contact | Communication Centre merck KGaA, Merck Serono, a division of Merck KGaA, 49 6151725200, service@merckgroup.com |
| Scientific contact | Communication Centre merck KGaA, Merck Serono, a division of Merck KGaA, 49 6151725200, service@merckgroup.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 | 30 August 2013 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|----------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 August 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

REFLEXION is a double blind extension of the study 27025 (NCT00404352) (REFLEX). The purpose of the study is to obtain long-term follow-up data in subjects with clinically definite multiple sclerosis (MS) and subjects with a first demyelinating event at high risk of converting to MS, treated with fetal bovine serum [FBS]-free/human serum albumin [HSA]-free formulation of interferon [IFN]-beta-1a (RNF).

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 22 December 2008 |
| 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 | Czech Republic: 64 |
| Country: Number of subjects enrolled | Estonia: 8 |
| Country: Number of subjects enrolled | Finland: 1 |
| Country: Number of subjects enrolled | France: 10 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Greece: 3 |
| Country: Number of subjects enrolled | Israel: 3 |
| Country: Number of subjects enrolled | Argentina: 5 |
| Country: Number of subjects enrolled | Austria: 2 |
| Country: Number of subjects enrolled | Belgium: 3 |
| Country: Number of subjects enrolled | Bulgaria: 36 |
| Country: Number of subjects enrolled | Canada: 10 |
| Country: Number of subjects enrolled | Croatia: 53 |
| Country: Number of subjects enrolled | Italy: 5 |
| Country: Number of subjects enrolled | Lebanon: 18 |
| Country: Number of subjects enrolled | Latvia: 1 |
| Country: Number of subjects enrolled | Morocco: 4 |
| Country: Number of subjects enrolled | Poland: 32 |
| Country: Number of subjects enrolled | Portugal: 1 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Romania: 34 |
| Country: Number of subjects enrolled | Russian Federation: 72 |
| Country: Number of subjects enrolled | Serbia: 17 |
| Country: Number of subjects enrolled | Slovakia: 3 |
| Country: Number of subjects enrolled | Spain: 14 |
| Worldwide total number of subjects | 402 |
| EEA total number of subjects | 273 |

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) | 1 |
| Adults (18-64 years) | 401 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects who were randomized in Study 27025 (NCT00404352) were eligible to enroll into extension Study 28981 (NCT00813709) whether or not they completed main study on Investigational Medicinal Product (IMP), or no treatment or received other disease-modifying drugs (DMDs) during course of main study. No re-randomization was done for this study.

Pre-assignment

Screening details:

517 subjects randomized in Study 27025 used in this study as integrated intention to treat (ITT) population. Out of the 517, 402 subjects took part in study 28981: 300 comprised the double blind (DB) population and 122 comprised the open label (OL) population (some subjects (20) were included in both populations).

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Overall Study |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo/RNF 44 microgram (mcg) Thrice Weekly (ITT population) |

Arm description:

Subjects who were initially randomized in study 27025 (REFLEX) to the placebo treatment group were switched to single dose of RNF injection administered subcutaneously 3 times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months or until conversion to CDMS whichever occurs first. After having converted to CDMS, subjects received OL study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 36 months. 84 subjects were initially assigned to DB RNF 44 mcg thrice weekly and 49 subjects were initially assigned to OL RNF 44 mcg thrice weekly (9 subjects from DB converted to CDMS and switched to OL period over course of this study).

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | RNF |
| Investigational medicinal product code | |
| Other name | Rebif |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

RNF was administered subcutaneously three times weekly at least 48 hours apart at a dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months.

| | |
|------------------|---|
| Arm title | RNF 44 mcg Once Weekly (ITT population) |
|------------------|---|

Arm description:

Single dose of RNF injection administered subcutaneously once weekly plus 2 matching placebo doses at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 36 months or until conversion to CDMS whichever occurs first. After having converted to CDMS, subjects received OL study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months. 117 subjects were initially assigned to DB RNF 44 mcg thrice weekly and 25 subjects were initially assigned to OL RNF 44 mcg thrice weekly (26 subjects from DB converted to CDMS and switched to OL period over course of this study).

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

| | |
|--|------------------------|
| Investigational medicinal product name | RNF |
| Investigational medicinal product code | |
| Other name | Rebif |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Single dose of RNF will be administered subcutaneously once weekly at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months.

| | |
|------------------|---|
| Arm title | RNF 44 mcg Thrice Weekly (ITT Population) |
|------------------|---|

Arm description:

Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 36 months or until conversion to CDMS whichever occurs first. After having converted to CDMS, subjects received OL study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months. 99 subjects were initially assigned to DB RNF 44 mcg thrice weekly and 28 subjects were initially assigned to OL RNF 44 mcg thrice weekly (18 subjects from DB converted to CDMS and switched to OL period over course of this study).

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | RNF |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Single dose of RNF was administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 microgram (mcg) for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months.

| Number of subjects in period 1 | Placebo/RNF 44 microgram (mcg) Thrice Weekly (ITT population) | RNF 44 mcg Once Weekly (ITT population) | RNF 44 mcg Thrice Weekly (ITT Population) |
|---------------------------------------|---|---|---|
| Started | 133 | 142 | 127 |
| Completed | 97 | 118 | 103 |
| Not completed | 36 | 24 | 24 |
| Premature treatment discontinuation | 24 | 13 | 16 |
| Unspecified | 7 | 8 | 5 |
| Lost to follow-up | 5 | 3 | 3 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Double blind period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

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

| | |
|------------------|--|
| Arm title | Placebo/RNF 44 mcg Thrice Weekly (DB Population) |
|------------------|--|

Arm description:

Subjects who were initially randomized in study 27025 (REFLEX) to the placebo treatment group were switched to single dose of fetal bovine serum [FBS]-free/human serum albumin [HSA]-free formulation of Interferon [IFN]-beta-1a (RNF) injection administered subcutaneously 3 times weekly at least 48 hours apart at a starting dose of 8.8 microgram (mcg) for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months or until conversion to clinically definite multiple sclerosis (CDMS) whichever occurs first.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | RNF |
| Investigational medicinal product code | |
| Other name | Rebif® |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

RNF was administered subcutaneously three times weekly at least 48 hours apart at a dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months.

| | |
|------------------|--|
| Arm title | RNF 44 mcg Once Weekly (DB Population) |
|------------------|--|

Arm description:

Single dose of RNF injection administered subcutaneously once weekly plus 2 matching placebo doses at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 60 months or until conversion to CDMS whichever occurs first.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | RNF |
| Investigational medicinal product code | |
| Other name | Rebif |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Single dose of RNF will be administered subcutaneously once weekly at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months.

| | |
|------------------|--|
| Arm title | RNF 44 mcg Thrice Weekly (DB Population) |
|------------------|--|

Arm description:

Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 60 months or until conversion to CDMS whichever occurs first.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | RNF |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Single dose of RNF was administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 microgram (mcg) for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months.

| Number of subjects in period 2^[1] | Placebo/RNF 44 mcg Thrice Weekly (DB Population) | RNF 44 mcg Once Weekly (DB Population) | RNF 44 mcg Thrice Weekly (DB Population) |
|---|--|--|--|
| Started | 84 | 117 | 99 |
| Completed | 53 | 76 | 68 |
| Not completed | 31 | 41 | 31 |
| Randomized but not treated | 1 | 3 | 1 |
| Switched to open label phase | 9 | 26 | 18 |
| Adverse event | 4 | 1 | 4 |
| Unspecified | - | 9 | 6 |
| Unspecified | 14 | - | - |
| Lost to follow-up | 3 | 2 | 2 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total of 402 subjects took part in study 28981: 300 comprised the double blind (DB) population and 122 comprised the open label (OL) population (some subjects (20) were included in both populations).

Period 3

| | |
|------------------------------|-------------------------|
| Period 3 title | Open Label |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo/RNF 44 mcg Thrice Weekly/OL RNF 44 Mcg Thrice Weekly |

Arm description:

Subjects after having converted to CDMS during study 28981 (REFLEXION), received open-label (OL) study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months. The subjects who were converted to CDMS in study 27025 (REFLEX) and were enrolled in this study continued receiving RNF 44 mcg three times weekly until 60 months. 49 subjects in OL period initially + 9 subjects from DB converted to CDMS during the study were included in this arm.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | RNF |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Single dose of RNF was administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 microgram (mcg) for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months.

| | |
|------------------|---|
| Arm title | RNF 44 mcg Once Weekly /OL RNF 44 mcg Thrice Weekly |
|------------------|---|

Arm description:

Subjects after having converted to CDMS during study 28981 (REFLEXION), received OL study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months. The subjects who were converted to CDMS in study 27025 (REFLEX)

and were enrolled in this study continued receiving RNF 44 mcg three times weekly until 60 months. 25 subjects in OL period initially + 26 subjects from DB converted to CDMS during the study were included in this arm.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | RNF |
| Investigational medicinal product code | |
| Other name | Rebif |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Single dose of RNF will be administered subcutaneously once weekly at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months.

| | |
|--|------------------------|
| Investigational medicinal product name | RNF |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Single dose of RNF was administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 microgram (mcg) for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months.

| | |
|------------------|--|
| Arm title | RNF 44 mcg Thrice Weekly/OL RNF 44 mcg Thrice Weekly |
|------------------|--|

Arm description:

Subjects after having converted to CDMS during study 28981 (REFLEXION), received OL study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months. The subjects who were converted to CDMS in study 27025 (REFLEX) and were enrolled in this study continued receiving RNF 44 mcg three times weekly until 60 months. 28 subjects in OL period initially + 18 subjects from DB converted to CDMS during the study were included in this arm.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | RNF |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Single dose of RNF was administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 microgram (mcg) for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months.

| Number of subjects in period 3^[2] | Placebo/RNF 44 mcg Thrice Weekly/OL RNF 44 Mcg Thrice Weekly | RNF 44 mcg Once Weekly /OL RNF 44 mcg Thrice Weekly | RNF 44 mcg Thrice Weekly/OL RNF 44 mcg Thrice Weekly |
|---|--|---|--|
| Started | 58 | 51 | 46 |
| Completed | 38 | 41 | 35 |
| Not completed | 20 | 10 | 11 |
| Adverse events | 5 | - | - |
| Randomized but not treated | 1 | - | 1 |
| Adverse event | - | 4 | 3 |

| | | | |
|------------------|----|---|---|
| Unspecified | 11 | 5 | 6 |
| Lack of efficacy | 3 | 1 | 1 |

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total of 402 subjects took part in study 28981: 300 comprised the double blind (DB) population and 122 comprised the open label (OL) population (some subjects (20) were included in both populations).

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Placebo/RNF 44 microgram (mcg) Thrice Weekly (ITT population) |
|-----------------------|---|

Reporting group description:

Subjects who were initially randomized in study 27025 (REFLEX) to the placebo treatment group were switched to single dose of RNF injection administered subcutaneously 3 times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months or until conversion to CDMS whichever occurs first. After having converted to CDMS, subjects received OL study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 36 months. 84 subjects were initially assigned to DB RNF 44 mcg thrice weekly and 49 subjects were initially assigned to OL RNF 44 mcg thrice weekly (9 subjects from DB converted to CDMS and switched to OL period over course of this study).

| | |
|-----------------------|---|
| Reporting group title | RNF 44 mcg Once Weekly (ITT population) |
|-----------------------|---|

Reporting group description:

Single dose of RNF injection administered subcutaneously once weekly plus 2 matching placebo doses at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 36 months or until conversion to CDMS whichever occurs first. After having converted to CDMS, subjects received OL study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months. 117 subjects were initially assigned to DB RNF 44 mcg thrice weekly and 25 subjects were initially assigned to OL RNF 44 mcg thrice weekly (26 subjects from DB converted to CDMS and switched to OL period over course of this study).

| | |
|-----------------------|---|
| Reporting group title | RNF 44 mcg Thrice Weekly (ITT Population) |
|-----------------------|---|

Reporting group description:

Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 36 months or until conversion to CDMS whichever occurs first. After having converted to CDMS, subjects received OL study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months. 99 subjects were initially assigned to DB RNF 44 mcg thrice weekly and 28 subjects were initially assigned to OL RNF 44 mcg thrice weekly (18 subjects from DB converted to CDMS and switched to OL period over course of this study).

| Reporting group values | Placebo/RNF 44 microgram (mcg) Thrice Weekly (ITT population) | RNF 44 mcg Once Weekly (ITT population) | RNF 44 mcg Thrice Weekly (ITT Population) |
|------------------------------------|---|---|---|
| Number of subjects | 133 | 142 | 127 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-------------|---------------|---------------|
| Age continuous Units: years arithmetic mean standard deviation | 31 ± 8.2 | 31.4 ± 8.2 | 31.8 ± 8.6 |
| Gender categorical Units: Subjects | | | |
| Female | 82 | 88 | 78 |
| Male | 51 | 54 | 49 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 402 | | |

| | | | |
|---|-----|--|--|
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 248 | | |
| Male | 154 | | |

End points

End points reporting groups

| | |
|-----------------------|---|
| Reporting group title | Placebo/RNF 44 microgram (mcg) Thrice Weekly (ITT population) |
|-----------------------|---|

Reporting group description:

Subjects who were initially randomized in study 27025 (REFLEX) to the placebo treatment group were switched to single dose of RNF injection administered subcutaneously 3 times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months or until conversion to CDMS whichever occurs first. After having converted to CDMS, subjects received OL study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 36 months. 84 subjects were initially assigned to DB RNF 44 mcg thrice weekly and 49 subjects were initially assigned to OL RNF 44 mcg thrice weekly (9 subjects from DB converted to CDMS and switched to OL period over course of this study).

| | |
|-----------------------|---|
| Reporting group title | RNF 44 mcg Once Weekly (ITT population) |
|-----------------------|---|

Reporting group description:

Single dose of RNF injection administered subcutaneously once weekly plus 2 matching placebo doses at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 36 months or until conversion to CDMS whichever occurs first. After having converted to CDMS, subjects received OL study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months. 117 subjects were initially assigned to DB RNF 44 mcg thrice weekly and 25 subjects were initially assigned to OL RNF 44 mcg thrice weekly (26 subjects from DB converted to CDMS and switched to OL period over course of this study).

| | |
|-----------------------|---|
| Reporting group title | RNF 44 mcg Thrice Weekly (ITT Population) |
|-----------------------|---|

Reporting group description:

Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 36 months or until conversion to CDMS whichever occurs first. After having converted to CDMS, subjects received OL study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months. 99 subjects were initially assigned to DB RNF 44 mcg thrice weekly and 28 subjects were initially assigned to OL RNF 44 mcg thrice weekly (18 subjects from DB converted to CDMS and switched to OL period over course of this study).

| | |
|-----------------------|--|
| Reporting group title | Placebo/RNF 44 mcg Thrice Weekly (DB Population) |
|-----------------------|--|

Reporting group description:

Subjects who were initially randomized in study 27025 (REFLEX) to the placebo treatment group were switched to single dose of fetal bovine serum [FBS]-free/human serum albumin [HSA]-free formulation of Interferon [IFN]-beta-1a (RNF) injection administered subcutaneously 3 times weekly at least 48 hours apart at a starting dose of 8.8 microgram (mcg) for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months or until conversion to clinically definite multiple sclerosis (CDMS) whichever occurs first.

| | |
|-----------------------|--|
| Reporting group title | RNF 44 mcg Once Weekly (DB Population) |
|-----------------------|--|

Reporting group description:

Single dose of RNF injection administered subcutaneously once weekly plus 2 matching placebo doses at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 60 months or until conversion to CDMS whichever occurs first.

| | |
|-----------------------|--|
| Reporting group title | RNF 44 mcg Thrice Weekly (DB Population) |
|-----------------------|--|

Reporting group description:

Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 60 months or until conversion to CDMS whichever occurs first.

| | |
|-----------------------|--|
| Reporting group title | Placebo/RNF 44 mcg Thrice Weekly/OL RNF 44 Mcg Thrice Weekly |
|-----------------------|--|

Reporting group description:

Subjects after having converted to CDMS during study 28981 (REFLEXION), received open-label (OL) study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for

next 2 weeks and finally 44 mcg until 60 months. The subjects who were converted to CDMS in study 27025 (REFLEX) and were enrolled in this study continued receiving RNF 44 mcg three times weekly until 60 months. 49 subjects in OL period initially + 9 subjects from DB converted to CDMS during the study were included in this arm.

| | |
|-----------------------|---|
| Reporting group title | RNF 44 mcg Once Weekly /OL RNF 44 mcg Thrice Weekly |
|-----------------------|---|

Reporting group description:

Subjects after having converted to CDMS during study 28981 (REFLEXION), received OL study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months. The subjects who were converted to CDMS in study 27025 (REFLEX) and were enrolled in this study continued receiving RNF 44 mcg three times weekly until 60 months. 25 subjects in OL period initially + 26 subjects from DB converted to CDMS during the study were included in this arm.

| | |
|-----------------------|--|
| Reporting group title | RNF 44 mcg Thrice Weekly/OL RNF 44 mcg Thrice Weekly |
|-----------------------|--|

Reporting group description:

Subjects after having converted to CDMS during study 28981 (REFLEXION), received OL study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months. The subjects who were converted to CDMS in study 27025 (REFLEX) and were enrolled in this study continued receiving RNF 44 mcg three times weekly until 60 months. 28 subjects in OL period initially + 18 subjects from DB converted to CDMS during the study were included in this arm.

| | |
|----------------------------|--|
| Subject analysis set title | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) |
|----------------------------|--|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Subjects who were initially randomized in study 27025 (REFLEX) to the placebo treatment group were switched to single dose of fetal bovine serum [FBS]-free/human serum albumin [HSA]-free formulation of Interferon [IFN]-beta-1a (RNF) injection administered subcutaneously 3 times weekly at least 48 hours apart at a starting dose of 8.8 microgram (mcg) for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 36 months or until conversion to clinically definite multiple sclerosis (CDMS) whichever occurs first. After having converted to CDMS, subjects received open-label (OL) study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months.

| | |
|----------------------------|--|
| Subject analysis set title | RNF 44 Mcg thrice Weekly (integrated ITT population) |
|----------------------------|--|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 36 months or until conversion to CDMS whichever occurs first. After having converted to CDMS, subjects received open-label (OL) study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months.

| | |
|----------------------------|--|
| Subject analysis set title | RNF 44 Mcg Once Weekly (integrated ITT population) |
|----------------------------|--|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Single dose of RNF injection administered subcutaneously once weekly plus 2 matching placebo doses at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 36 months or until conversion to CDMS whichever occurs first. After having converted to CDMS, subjects received open-label (OL) study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months.

| | |
|----------------------------|---|
| Subject analysis set title | Placebo/RNF 44 Mcg thrice Weekly (integrated DB population) |
|----------------------------|---|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Subjects who were initially randomized in study 27025 (REFLEX) to the placebo treatment group were switched to single dose of fetal bovine serum [FBS]-free/human serum albumin [HSA]-free formulation of Interferon [IFN]-beta-1a (RNF) injection administered subcutaneously 3 times weekly at least 48 hours apart at a starting dose of 8.8 microgram (mcg) for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months or until conversion to clinically definite multiple sclerosis (CDMS) whichever occurs first.

| | |
|----------------------------|---|
| Subject analysis set title | RNF 44 Mcg Once Weekly (integrated DB population) |
|----------------------------|---|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Single dose of RNF injection administered subcutaneously once weekly plus 2 matching placebo doses at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 60 months or until conversion to CDMS whichever occurs first.

| | |
|----------------------------|---|
| Subject analysis set title | RNF 44 Mcg thrice Weekly (integrated DB population) |
|----------------------------|---|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 36 months or until conversion to CDMS whichever occurs first.

| | |
|----------------------------|---|
| Subject analysis set title | Placebo/RNF 44 Mcg thrice Weekly (DB safety population) |
|----------------------------|---|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Subjects who were initially randomized in study 27025 (REFLEX) to the placebo treatment group were switched to single dose of fetal bovine serum [FBS]-free/human serum albumin [HSA]-free formulation of Interferon [IFN]-beta-1a (RNF) injection administered subcutaneously 3 times weekly at least 48 hours apart at a starting dose of 8.8 microgram (mcg) for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months or until conversion to clinically definite multiple sclerosis (CDMS) whichever occurs first.

| | |
|----------------------------|---|
| Subject analysis set title | RNF 44 Mcg Once Weekly (DB safety population) |
|----------------------------|---|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Single dose of RNF injection administered subcutaneously once weekly plus 2 matching placebo doses at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 60 months or until conversion to CDMS whichever occurs first.

| | |
|----------------------------|---|
| Subject analysis set title | RNF 44 Mcg thrice Weekly (DB safety population) |
|----------------------------|---|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 60 months or until conversion to CDMS whichever occurs first.

Primary: Time to Conversion to Clinically Definite Multiple Sclerosis (CDMS) Defined by Either a Second Attack or a Sustained Increase (Greater Than or Equal to 1.5 Points) in the Expanded Disability Status Scale (EDSS) Score up to 36 months

| | |
|-----------------|--|
| End point title | Time to Conversion to Clinically Definite Multiple Sclerosis (CDMS) Defined by Either a Second Attack or a Sustained Increase (Greater Than or Equal to 1.5 Points) in the Expanded Disability Status Scale (EDSS) Score up to 36 months |
|-----------------|--|

End point description:

CDMS was defined by the occurrence of a second attack or relapse over 36 months in subjects who presented with clinically isolated syndrome (CIS) accompanied by an abnormal magnetic resonance imaging (MRI) scan. EDSS assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to multiple sclerosis [MS]) was calculated. Time to conversion to CDMS was represented by Kaplan-Meier estimates of the cumulative percentage (%) of subjects with CDMS. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352).

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

End point timeframe:

Baseline (Day 1 of Study 27025) up to 36 Months

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|---|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: Cumulative % of subjects with CDMS | | | | |
| number (confidence interval 95%) | 41.3 (33.5 to 49.1) | 27.6 (20.6 to 34.6) | 27.1 (19.9 to 34.3) | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis 1 for TIme to CDMS |
| Comparison groups | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) v RNF 44 Mcg thrice Weekly (integrated ITT population) |
| Number of subjects included in analysis | 342 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.002 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.555 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.378 |
| upper limit | 0.816 |

| | |
|---|---|
| Statistical analysis title | Statistical analysis 2 for TIme to CDMS |
| Comparison groups | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) v RNF 44 Mcg Once Weekly (integrated ITT population) |
| Number of subjects included in analysis | 346 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.006 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.573 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.391 |
| upper limit | 0.839 |

| | |
|---|---|
| Statistical analysis title | Statistical analysis 3 for Time to CDMS |
| Comparison groups | RNF 44 Mcg Once Weekly (integrated ITT population) v RNF 44 Mcg thrice Weekly (integrated ITT population) |
| Number of subjects included in analysis | 346 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.941 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.993 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.654 |
| upper limit | 1.51 |

Secondary: Time to confirmed Expanded Disability Status Scale (EDSS) progression up to 36 months

| | |
|--|---|
| End point title | Time to confirmed Expanded Disability Status Scale (EDSS) progression up to 36 months |
| End point description: | |
| EDSS assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to MS) was calculated. A confirmed EDSS progression was defined EDSS greater than or equal to 1.0 point confirmed during a visit performed 6 months later. Time to confirmed EDSS progression was represented by Kaplan-Meier estimates of the cumulative percentage (%) of subjects with confirmed EDSS progression. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352). | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Day 1 of Study 27025) up to 36 Months | |

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|--|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: % of subjects with EDSS progression | | | | |
| number (not applicable) | 7.5 | 11.8 | 13.2 | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Statistical Analysis 1 for EDSS progression |
| Comparison groups | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) v RNF 44 Mcg thrice Weekly (integrated ITT population) |

| | |
|---|---------------|
| Number of subjects included in analysis | 342 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.205 |
| Method | Logrank |
| Confidence interval | |
| level | 95 % |

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 2 for EDSS progression |
| Comparison groups | RNF 44 Mcg Once Weekly (integrated ITT population) v RNF 44 Mcg thrice Weekly (integrated ITT population) |
| Number of subjects included in analysis | 346 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.629 |
| Method | Logrank |
| Confidence interval | |
| level | 95 % |

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 3 for EDSS progression |
| Comparison groups | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) v RNF 44 Mcg Once Weekly (integrated ITT population) |
| Number of subjects included in analysis | 346 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.263 |
| Method | Logrank |
| Confidence interval | |
| level | 95 % |

Secondary: Number of Combined Unique Active (CUA) Lesions, New Time Constant 2 (T2) Lesions, new Gadolinium Enhanced (Gd+) Lesions and New Time Constant 1 (T1) Lesions Per Subjects Per Scan at Month 36

| | |
|-----------------|--|
| End point title | Number of Combined Unique Active (CUA) Lesions, New Time Constant 2 (T2) Lesions, new Gadolinium Enhanced (Gd+) Lesions and New Time Constant 1 (T1) Lesions Per Subjects Per Scan at Month 36 |
|-----------------|--|

End point description:

Number of CUA lesions, new T2 lesions, new Gd+ lesions and new T1 lesions were measured by using MRI scans. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352) and who were evaluable for this measure at this time point.

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

End point timeframe:

Month 36

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|--------------------------------------|--|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 124 | 133 | 114 | |
| Units: lesions | | | | |
| arithmetic mean (standard deviation) | | | | |
| CUA Lesions | 1.02 (± 1.85) | 1.83 (± 3.317) | 1.63 (± 5.947) | |
| New T2 Lesions | 0.83 (± 1.545) | 1.39 (± 2.573) | 1.19 (± 4.217) | |
| New Gd+ Lesions | 0.17 (± 0.506) | 0.4 (± 1.354) | 0.41 (± 1.754) | |
| New T1 Lesions | 0.69 (± 1.721) | 1.09 (± 2.482) | 0.91 (± 4.143) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Time Constant 1 (T1) Hypointense Lesion Volume and Time Constant 2 (T2) Lesion Volume at Month 36

| | |
|------------------------|---|
| End point title | Change From Baseline in Time Constant 1 (T1) Hypointense Lesion Volume and Time Constant 2 (T2) Lesion Volume at Month 36 |
| End point description: | Change from baseline in lesion volume was measured by using MRI scans for T1 hypointense lesions and T2 lesions at Month 36. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352). "n" signifies those subjects who were evaluated for this measure at the specified time point for each arm group respectively. |
| End point type | Secondary |
| End point timeframe: | Baseline (Day 1 of Study 27025), Month 36 |

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|---|--|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: cubic millimeter (mm ³) | | | | |
| arithmetic mean (standard deviation) | | | | |
| T1 lesion volume at Baseline (n=171,175,171) | 670.3 (± 1054.1) | 774.8 (± 1288) | 675 (± 1049.9) | |
| Change in T1 lesion volume Month 36(n=124,133,114) | 303.2 (± 1034.6) | 272 (± 921.4) | 133.3 (± 763.5) | |
| T2 lesion volume at Baseline (n=171,175,171) | 3334.9 (± 3990.4) | 3853.1 (± 4716.7) | 3110.5 (± 3410.7) | |

| | | | | |
|--|-----------------|------------------|-------------------|--|
| Change in T2 lesion volume Month 36(n=124,133,114) | -3.8 (± 2101.8) | -56.9 (± 2436.3) | -398.1 (± 1415.4) | |
|--|-----------------|------------------|-------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change From Baseline in Brain Volume at Month 36

| | |
|---|--|
| End point title | Percent change From Baseline in Brain Volume at Month 36 |
| End point description: Percent change in brain volume was measured by using MRI scans. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352) and who were evaluable for this measure at this time point. | |
| End point type | Secondary |
| End point timeframe: Baseline (Day 1 of Study 27025), Month 36 | |

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 120 | 132 | 112 | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | -1.02 (± 1.248) | -0.86 (± 1.073) | -1.14 (± 1.321) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with conversion to McDonald multiple sclerosis (MS) up to 36 Months

| | |
|--|--|
| End point title | Percentage of subjects with conversion to McDonald multiple sclerosis (MS) up to 36 Months |
| End point description: The McDonald criteria use dissemination in time and space established by MRI findings to provide a clinical diagnosis for MS. Dissemination in time is established by a new T2 or Gd+ lesion found on a repeat MRI. Dissemination in space is established by the presence of any 3 of the following: 1 Gd+ lesion or 9 T2 bright lesions if there is no enhancement; greater than or equal to 1 infratentorial lesion; greater than or equal to 1 juxtacortical lesion; greater than or equal to 3 periventricular lesions. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352). | |
| End point type | Secondary |
| End point timeframe: Baseline (Day 1 of Study 27025) up to CDMS conversion and/or up to 36 Months | |

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|-------------------------------|--|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 84.2 | 76 | 66.7 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Paced Auditory Serial Addition Test 3 (PASAT-3) Score at Month 36

| | |
|---|---|
| End point title | Change From Baseline in Paced Auditory Serial Addition Test 3 (PASAT-3) Score at Month 36 |
| End point description: | |
| The Paced Auditory Serial Addition Test (PASAT) is a measure of cognitive function that specifically assesses auditory information processing speed and flexibility, as well as calculation ability. Score ranges from '0-60'. Higher scores reflect better neurological function and a positive change from baseline indicates improvement. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352). "n" signifies those subjects who were evaluated for this measure at the specified time point for each arm group respectively. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Day of Study 27025), Month 36 | |

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|--------------------------------------|--|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=171,175,171) | 0.0358 (± 0.8787) | -0.0909 (± 1.1223) | 0.0031 (± 1.1387) | |
| Change at Month 36 (n=123,135,118) | 0.3483 (± 0.6949) | 0.5044 (± 0.7588) | 0.4515 (± 0.9164) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Relapse-Free Subjects at Month 36

| | |
|--|---|
| End point title | Percentage of Relapse-Free Subjects at Month 36 |
| End point description: A relapse was defined as the development of new or the exacerbation of existing neurological symptoms or signs, in the absence of fever, lasting for 24 hours and with a previous period for more than 30 days with a stable or an improving condition. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352). | |
| End point type | Secondary |
| End point timeframe: Month 36 | |

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|-------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 42.7 | 58.3 | 51.5 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in expanded disability status scale (EDSS) score at month 36

| | |
|---|---|
| End point title | Change from baseline in expanded disability status scale (EDSS) score at month 36 |
| End point description: EDSS assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to MS) was calculated. The change in EDSS score at Month 36 was calculated as EDSS score at Month 36 minus EDSS score at baseline. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352). "n" signifies those subjects who were evaluated for this measure at the specified time point for each arm group respectively. | |
| End point type | Secondary |
| End point timeframe: Baseline (Day of Study 27025), Month 36 | |

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|--------------------------------------|--|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=171,175,171) | 1.53 (± 0.77) | 1.5 (± 0.72) | 1.51 (± 0.83) | |
| Change at Month 36 (n=120,136,116) | -0.21 (± 0.93) | -0.11 (± 0.96) | -0.09 (± 0.9) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Multiple Sclerosis Functional Composite (MSFC) Score at Month 36

| | |
|-----------------|--|
| End point title | Change From Baseline in Multiple Sclerosis Functional Composite (MSFC) Score at Month 36 |
|-----------------|--|

End point description:

The MSFC is a multidimensional clinical outcome measure of three sub-tests; Timed 25-Foot Walk, 9-Hole Peg Test and Paced Auditory Serial Addition Test-3(PASAT-3). The Timed 25-Foot Walk is a quantitative measure of lower extremity function. The 9-Hole Peg Test is a quantitative measure of upper extremity function. The PASAT is a measure of cognitive function that specifically assesses auditory information processing speed and flexibility, as well as calculation ability. Standardized results (Z-scores) of these sub-tests and the overall MSFC Z-score as an average of these 3 Z-scores was calculated. Higher Z-scores reflect better neurological function and a positive change from baseline indicates improvement. An increase in score indicates an improvement (range -3 to +3). Data was presented for integrated ITT population of 27025 (NCT00404352) study. "n" signifies those subjects who were evaluated for this measure at the specified time point for each arm respectively.

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

End point timeframe:

Baseline (Day 1 of Study 27025), Month 36

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|---|--|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: Z-score | | | | |
| arithmetic mean (standard deviation) | | | | |
| MFSC score at Baseline (n=171,175,171) | 0.0352 (± 0.5844) | 0.0071 (± 0.6653) | -0.0575 (± 0.6226) | |
| Change at Month 36 (n=123,135,118) | 0.1993 (± 0.4863) | 0.2529 (± 0.5794) | 0.3074 (± 0.6071) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Numbers of Subjects With Binding Antibodies (BAb) and Neutralizing Antibody (NAb) at Month 36

| | |
|-----------------|---|
| End point title | Numbers of Subjects With Binding Antibodies (BAb) and Neutralizing Antibody (NAb) at Month 36 |
|-----------------|---|

End point description:

BABs are all antibodies which are capable of binding to the investigational drug molecule (RNF) irrespective of their binding site. NABs are defined as a subgroup of BABs which bind to the active sites of the RNF and therefore neutralize its potency. NABs were detected using a viral cytopathic assay. BABs were measured by using an ELISA (Enzyme-linked immunosorbent assay). Data has been presented as per planned analysis for integrated DB population which included all subjects who received at least one dose of DB treatment in REFLEX study 27025 (NCT00404352) and who were evaluable for this measure at this time point.

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

End point timeframe:

Month 36

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated DB population) | RNF 44 Mcg Once Weekly (integrated DB population) | RNF 44 Mcg thrice Weekly (integrated DB population) | |
|-----------------------------|---|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 118 | 131 | 118 | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| BAb- | 77 | 97 | 88 | |
| BAb+ | 41 | 34 | 30 | |
| NAb- | 100 | 109 | 99 | |
| NAb+ | 18 | 22 | 19 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs) and AEs leading to treatment discontinuation

| | |
|-----------------|--|
| End point title | Number of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs) and AEs leading to treatment discontinuation |
|-----------------|--|

End point description:

An AE was defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to baseline during a clinical study with an Investigational Medicinal Product (IMP), regardless of causal relationship and even if no IMP has been administered. SAE: Any AE that resulted in death; was life threatening; resulted in persistent/significant disability/incapacity; resulted in/prolonged an existing in-patient hospitalization; was a congenital anomaly/birth defect; or was a medically important condition. DB Safety Population 28981 (REFLEXION) included all the subjects who discontinued DB treatment in REFLEX study 27025 (NCT00404352) and were enrolled in 28981 (REFLEXION) study and received at least one dose of DB treatment in this study and who were evaluable for this measure.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Month 24 up to Month 36 (DB treatment period for study 28981 (REFLEXION)) | |

| End point values | Placebo/RNF 44 Mcg thrice Weekly (DB safety population) | RNF 44 Mcg Once Weekly (DB safety population) | RNF 44 Mcg thrice Weekly (DB safety population) | |
|--------------------------------|---|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 84 | 117 | 99 | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| AEs | 79 | 67 | 45 | |
| SAEs | 3 | 2 | 4 | |
| AEs leading to discontinuation | 2 | 0 | 2 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to conversion to Clinically Definite Multiple Sclerosis (CDMS) defined by either a second attack or a sustained increase (greater than or equal to 1.5 points) in the Expanded Disability Status Scale (EDSS) score up to Month 60

| | |
|-----------------|---|
| End point title | Time to conversion to Clinically Definite Multiple Sclerosis (CDMS) defined by either a second attack or a sustained increase (greater than or equal to 1.5 points) in the Expanded Disability Status Scale (EDSS) score up to Month 60 |
|-----------------|---|

End point description:

CDMS was defined by the occurrence of a second attack or relapse over 60 months in subjects who presented with clinically isolated syndrome (CIS) accompanied by an abnormal magnetic resonance imaging (MRI) scan. EDSS assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to multiple sclerosis [MS]) was calculated. Time to conversion to CDMS was represented by Kaplan-Meier estimates of the cumulative percentage (%) of subjects with CDMS. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352).

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Day 1 of Study 27025) up to 60 Months | |

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|---|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: Cumulative % of subjects with CDMS | | | | |

| | | | | |
|----------------------------------|---------------------|---------------------|---------------------|--|
| number (confidence interval 95%) | 44.6 (36.6 to 52.6) | 40.7 (32.8 to 48.6) | 39.2 (30.8 to 47.6) | |
|----------------------------------|---------------------|---------------------|---------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Time to confirmed Expanded Disability Status Scale (EDSS) progression up to 60 months

| | |
|--|---|
| End point title | Time to confirmed Expanded Disability Status Scale (EDSS) progression up to 60 months |
| End point description: EDSS assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to MS) was calculated. A confirmed EDSS progression was defined EDSS greater than or equal to 1.0 point confirmed during a visit performed 6 months later. Time to confirmed EDSS progression was represented by Kaplan-Meier estimates of the cumulative percentage (%) of subjects with confirmed EDSS progression. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352). | |
| End point type | Secondary |
| End point timeframe: Baseline (Day 1 of Study 27025) up to 60 Months | |

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|--|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: % of subjects with EDSS progression | | | | |
| number (not applicable) | 11 | 18.7 | 18.4 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Combined Unique Active (CUA) Lesions, New Time Constant 2 (T2) Lesions, New Gadolinium Enhanced (Gd+) Lesions and New T1 Lesions Per Subject Per Scan at Month 60

| | |
|--|---|
| End point title | Number of Combined Unique Active (CUA) Lesions, New Time Constant 2 (T2) Lesions, New Gadolinium Enhanced (Gd+) Lesions and New T1 Lesions Per Subject Per Scan at Month 60 |
| End point description: Number of CUA lesions, new T2 lesions, new Gd+ Lesions and new T1 lesions were measured by using MRI scans. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352). "n" signifies those subjects who were evaluated for this measure at the specified time point for each arm group | |

respectively.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Month 60 | |

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|--------------------------------------|--|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: lesions | | | | |
| arithmetic mean (standard deviation) | | | | |
| CUA Lesions (n=102, 121, 110) | 1.46 (± 3.394) | 1.6 (± 3.542) | 1.94 (± 4.803) | |
| New T2 Lesions (n=102, 121, 110) | 1.17 (± 2.576) | 1.17 (± 2.628) | 1.35 (± 3.284) | |
| New Gd+ Lesions (n=102, 121, 110) | 0.24 (± 0.823) | 0.36 (± 1.225) | 0.48 (± 1.618) | |
| New T1 Lesions (n=102, 120, 110) | 0.57 (± 1.656) | 0.69 (± 1.659) | 0.71 (± 1.917) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Time Constant 1 (T1) Hypointense Volume, and Time Constant 2 (T2) Lesion Volume at Month 60

| | |
|-----------------|---|
| End point title | Change From Baseline in Time Constant 1 (T1) Hypointense Volume, and Time Constant 2 (T2) Lesion Volume at Month 60 |
|-----------------|---|

End point description:

Change from baseline in lesion volume was measured by using MRI scans for T1 hypointense lesions and T2 lesions. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352). "n" signifies those subjects who were evaluated for this measure at the specified time point for each arm group respectively.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Day 1 of Study 27025), Month 60 | |

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|---|--|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: mm ³ | | | | |
| arithmetic mean (standard deviation) | | | | |
| T1 lesion volume at Baseline (n=171,175,171) | 670.3 (± 1054.1) | 774.8 (± 1288) | 675 (± 1049.9) | |

| | | | | |
|--|-------------------|-------------------|-------------------|--|
| Change at Month 60 (n=102,120,110) | 415 (± 1080.3) | 412.3 (± 1020.8) | 261.8 (± 1006.1) | |
| T2 lesion volume at Baseline (n=171,175,171) | 3334.9 (± 3990.4) | 3853.1 (± 4716.7) | 3110.5 (± 3410.7) | |
| Change at Month 60 (n=102,121,110) | 119.4 (± 2225.2) | 25 (± 2827.1) | -188.5 (± 2576.1) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in Brain Volume at month 60

| | |
|---|--|
| End point title | Percent change from baseline in Brain Volume at month 60 |
| End point description: Percent Change in brain volume was measured by using MRI scans. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352) and who were evaluable for this measure at this time point. | |
| End point type | Secondary |
| End point timeframe: Baseline (Day 1 of Study 27025), Month 60 | |

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 98 | 120 | 110 | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | -1.82 (± 1.494) | -1.54 (± 1.378) | -2.03 (± 1.644) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Conversion to McDonald Multiple Sclerosis (MS) at Month 60

| | |
|--|--|
| End point title | Percentage of Subjects With Conversion to McDonald Multiple Sclerosis (MS) at Month 60 |
| End point description: The McDonald criteria use dissemination in time and space established by MRI findings to provide a clinical diagnosis for MS. Dissemination in time is established by a new T2 or Gd+ lesion found on a repeat MRI. Dissemination in space is established by the presence of any 3 of the following: 1 Gd+ lesion or 9 T2 bright lesions if there is no enhancement; greater than or equal to 1 infratentorial lesion; greater than or equal to 1 juxtacortical lesion; greater than or equal to 3 periventricular lesions. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352). | |
| End point type | Secondary |

End point timeframe:

Month 60

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|-------------------------------|--|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 84.2 | 82.9 | 72.5 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Paced Auditory Serial Addition Test 3 (PASAT-3) Score at Month 60

| | |
|-----------------|---|
| End point title | Change From Baseline in Paced Auditory Serial Addition Test 3 (PASAT-3) Score at Month 60 |
|-----------------|---|

End point description:

The PASAT is a measure of cognitive function that specifically assesses auditory information processing speed and flexibility, as well as calculation ability. Score ranges from '0-60'. Higher scores reflect better neurological function and a positive change from baseline indicates improvement. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352). "n" signifies those subjects who were evaluated for this measure at the specified time point for each arm group respectively.

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

End point timeframe:

Baseline (Day 1 of Study 27025), Month 60

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|--------------------------------------|--|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=171, 175, 171) | 0.0358 (± 0.8787) | -0.0909 (± 1.1223) | 0.0031 (± 1.1387) | |
| Change at Month 60 (n=112, 132, 118) | 0.4109 (± 0.6844) | 0.4785 (± 0.9886) | 0.4608 (± 0.863) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Relapse-Free Subjects at Month 60

| | |
|-----------------|---|
| End point title | Percentage of Relapse-Free Subjects at Month 60 |
|-----------------|---|

End point description:

A relapse was defined as the development of new or the exacerbation of existing neurological symptoms or signs, in the absence of fever, lasting for 24 hours and with a previous period for more than 30 days with a stable or an improving condition. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352).

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

End point timeframe:

Month 60

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|-------------------------------|--|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 34.5 | 45.1 | 40.9 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Expanded Disability Status scale (EDSS) score at Month 60

| | |
|-----------------|---|
| End point title | Change From Baseline in Expanded Disability Status scale (EDSS) score at Month 60 |
|-----------------|---|

End point description:

EDSS assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to MS) was calculated. The change in EDSS score at Month 60 was calculated as EDSS score at Month 60 minus EDSS score at baseline. Data has been presented as per planned analysis for integrated ITT population which included all subjects who were randomized in REFLEX study 27025 (NCT00404352). "n" signifies those subjects who were evaluated for this measure at the specified time point for each arm group respectively.

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

End point timeframe:

Baseline (Day 1 of Study 27025), Month 60

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|--------------------------------------|--|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=171,175,171) | 1.53 (± 0.77) | 1.5 (± 0.72) | 1.51 (± 0.83) | |
| Change at Month 60 (n=111,133,117) | -0.11 (± 0.94) | -0.01 (± 1.01) | 0.04 (± 1.02) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Multiple Sclerosis Functional Composite (MSFC) Score at Month 60

| | |
|-----------------|--|
| End point title | Change From Baseline in Multiple Sclerosis Functional Composite (MSFC) Score at Month 60 |
|-----------------|--|

End point description:

The MSFC is a multidimensional clinical outcome measure of three sub-tests; Timed 25-Foot Walk, 9-Hole Peg Test and Paced Auditory Serial Addition Test-3(PASAT-3). The Timed 25-Foot Walk is a quantitative measure of lower extremity function. The 9-Hole Peg Test is a quantitative measure of upper extremity function. The PASAT is a measure of cognitive function that specifically assesses auditory information processing speed and flexibility, as well as calculation ability. Standardized results (Z-scores) of these sub-tests and the overall MSFC Z-score as an average of these 3 Z-scores was calculated. Higher Z-scores reflect better neurological function and a positive change from baseline indicates improvement. An increase in score indicates an improvement (range -3 to +3). Data was presented for integrated ITT population of 27025 (NCT00404352) study. "n" signifies those subjects who were evaluated for this measure at the specified time point for each arm respectively.

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

End point timeframe:

Baseline (Day 1 of Study 27025), Month 60

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated ITT population) | RNF 44 Mcg Once Weekly (integrated ITT population) | RNF 44 Mcg thrice Weekly (integrated ITT population) | |
|---|--|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 171 | 175 | 171 | |
| Units: Z-score | | | | |
| arithmetic mean (standard deviation) | | | | |
| MFSC score at Baseline (n=171,175,171) | -0.0575 (± 0.6226) | 0.0071 (± 0.6653) | 0.0352 (± 0.5844) | |
| Change at Month 60 (n=112,132,132) | 0.2192 (± 0.6229) | 0.2213 (± 0.5602) | 0.229 (± 0.4824) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Numbers of Subjects with Binding Antibodies (BAb) and Neutralizing Antibody (NAb) at Month 60

| | |
|-----------------|---|
| End point title | Numbers of Subjects with Binding Antibodies (BAb) and Neutralizing Antibody (NAb) at Month 60 |
|-----------------|---|

End point description:

BAbs are all antibodies which are capable of binding to the RNF irrespective of their binding site. NABs are defined as a subgroup of BAbS which bind to the active sites of the RNF and therefore neutralize its potency. NABs were detected using a viral cytopathic assay. BAbS were measured by using an ELISA. Data has been presented as per planned analysis for integrated DB population which included all subjects who received at least one dose of DB treatment in REFLEX study 27025 (NCT00404352) and who were evaluable for this measure at this time point.

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

End point timeframe:

Month 60

| End point values | Placebo/RNF 44 Mcg thrice Weekly (integrated DB population) | RNF 44 Mcg Once Weekly (integrated DB population) | RNF 44 Mcg thrice Weekly (integrated DB population) | |
|-----------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 115 | 130 | 115 | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| BAb- | 89 | 99 | 100 | |
| BAb+ | 25 | 30 | 15 | |
| BAb (Missing) | 1 | 1 | 0 | |
| Nab- | 97 | 110 | 102 | |
| Nab+ | 18 | 20 | 13 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs) and AEs leading to treatment discontinuation

| | |
|-----------------|--|
| End point title | Number of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs) and AEs leading to treatment discontinuation |
|-----------------|--|

End point description:

An AE was defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to baseline during a clinical study with an Investigational Medicinal Product (IMP), regardless of causal relationship and even if no IMP has been administered. SAE: Any AE that resulted in death; was life threatening; resulted in persistent/significant disability/incapacity; resulted in/prolonged an existing in-patient hospitalization; was a congenital anomaly/birth defect; or was a medically important condition.

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

End point timeframe:
Month 24 up to Month 60

| End point values | Placebo/RNF 44 Mcg thrice Weekly (DB safety population) | RNF 44 Mcg Once Weekly (DB safety population) | RNF 44 Mcg thrice Weekly (DB safety population) | |
|--------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 84 | 117 | 99 | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| AEs | 70 | 96 | 84 | |
| SAEs | 7 | 7 | 9 | |
| AEs leading to discontinuation | 3 | 0 | 2 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Month 24 to 60 for both DB safety population and OL safety population

Adverse event reporting additional description:

An adverse event (AE) was defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to baseline during a clinical study with IMP, regardless of causal relationship and even if no IMP has been administered.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Placebo/RNF 44 Mcg thrice Weekly (DB population) |
|-----------------------|--|

Reporting group description:

Subjects who were initially randomized in study 27025 (REFLEX) to the placebo treatment group were switched to single dose of fetal bovine serum [FBS]-free/human serum albumin [HSA]-free formulation of Interferon [IFN]-beta-1a (RNF) injection administered subcutaneously 3 times weekly at least 48 hours apart at a starting dose of 8.8 microgram (mcg) for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months or until conversion to clinically definite multiple sclerosis (CDMS) whichever occurs first.

| | |
|-----------------------|--|
| Reporting group title | RNF 44 Mcg Once Weekly (DB population) |
|-----------------------|--|

Reporting group description:

Single dose of RNF injection administered subcutaneously once weekly plus 2 matching placebo doses at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 60 months or until conversion to CDMS whichever occurs first.

| | |
|-----------------------|--|
| Reporting group title | RNF 44 Mcg thrice Weekly (DB population) |
|-----------------------|--|

Reporting group description:

Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and then 44 mcg until 60 months or until conversion to CDMS whichever occurs first.

| | |
|-----------------------|--|
| Reporting group title | Placebo/RNF 44 Mcg thrice Weekly/OL RNF 44 Mcg thrice weekly |
|-----------------------|--|

Reporting group description:

Subjects after having converted to CDMS during study 28981 (REFLEXION), received open-label (OL) study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months. The subjects who were converted to CDMS in study 27025 (REFLEX) and were enrolled in this study continued receiving RNF 44 mcg three times weekly until 60 months.

| | |
|-----------------------|---|
| Reporting group title | RNF 44 Mcg Once Weekly /OL RNF 44 Mcg thrice Weekly |
|-----------------------|---|

Reporting group description:

Subjects after having converted to CDMS during study 28981 (REFLEXION), received OL study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months. The subjects who were converted to CDMS in study 27025 (REFLEX) and were enrolled in this study continued receiving RNF 44 mcg three times weekly until 60 months.

| | |
|-----------------------|--|
| Reporting group title | RNF 44 Mcg thrice Weekly/OL RNF 44 Mcg thrice Weekly |
|-----------------------|--|

Reporting group description:

Subjects after having converted to CDMS during study 28981 (REFLEXION), received OL study treatment with RNF. Single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 60 months. The subjects who were converted to CDMS in study 27025 (REFLEX) and were enrolled in this study continued receiving RNF 44 mcg three times weekly until 60 months.

| Serious adverse events | Placebo/RNF 44 Mcg thrice Weekly (DB population) | RNF 44 Mcg Once Weekly (DB population) | RNF 44 Mcg thrice Weekly (DB population) |
|--|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 84 (8.33%) | 7 / 117 (5.98%) | 9 / 99 (9.09%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cervix carcinoma stage 0 | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign neoplasm of thyroid gland | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 0 / 99 (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 |
| Malignant melanoma in situ | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine leiomyoma | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 1 / 117 (0.85%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Venous insufficiency | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 117 (0.85%) | 0 / 99 (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 |
| Hypertension | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 0 / 99 (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 |
| Surgical and medical procedures | | | |
| Appendicectomy | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 117 (0.85%) | 0 / 99 (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 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion missed | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 117 (0.85%) | 0 / 99 (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 |
| Abortion spontaneous | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foetal distress syndrome | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Fibula fracture | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 117 (0.00%) | 0 / 99 (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 |
| Post procedural fistula | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 117 (0.00%) | 0 / 99 (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 |
| Congenital, familial and genetic disorders | | | |
| Foetal chromosome abnormality | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 117 (0.85%) | 0 / 99 (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 |
| Cardiac disorders | | | |
| Angina stable | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute coronary syndrome | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 0 / 99 (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 | | | |
| Lumbar radiculopathy | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 0 / 99 (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 | | | |
| Vestibular disorder | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 117 (0.85%) | 0 / 99 (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 | | | |
| Eye haemorrhage | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Enterovesical fistula | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 117 (0.00%) | 0 / 99 (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 |
| Melaena | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 117 (0.00%) | 0 / 99 (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 |
| Abdominal pain | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 0 / 99 (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 |
| Abdominal pain upper | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 0 / 99 (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 | | | |
| Urticaria | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 117 (0.00%) | 0 / 99 (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 | | | |
| Nephrolithiasis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 117 (0.00%) | 0 / 99 (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 colic | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 117 (0.00%) | 0 / 99 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Osteoarthritis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 1 / 99 (1.01%) |
| 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 | | | |
| Abscess intestinal | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 117 (0.85%) | 0 / 99 (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 |
| Endometritis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 117 (0.85%) | 0 / 99 (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 |
| Salpingo-oophoritis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 117 (0.00%) | 0 / 99 (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 |
| Peritonsillar abscess | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 117 (0.00%) | 0 / 99 (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 | Placebo/RNF 44 Mcg thrice Weekly/OL RNF 44 Mcg thrice weekly | RNF 44 Mcg Once Weekly /OL RNF 44 Mcg thrice Weekly | RNF 44 Mcg thrice Weekly/OL RNF 44 Mcg thrice Weekly |
|---|--|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 3 / 51 (5.88%) | 4 / 46 (8.70%) |

| | | | |
|---|----------------|----------------|----------------|
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cervix carcinoma stage 0 | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 |
| Benign neoplasm of thyroid gland | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 1 / 46 (2.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma in situ | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 |
| Uterine leiomyoma | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 | | | |
| Venous insufficiency | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 |
| Hypertension | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 51 (1.96%) | 0 / 46 (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 |
| Surgical and medical procedures | | | |
| Appendectomy | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion missed | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 1 / 46 (2.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abortion spontaneous | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 |
| Foetal distress syndrome | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 | | | |
| Fibula fracture | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 |
| Post procedural fistula | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 |
| Congenital, familial and genetic disorders | | | |
| Foetal chromosome abnormality | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 | | | |
| Angina stable | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 coronary syndrome | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 51 (0.00%) | 0 / 46 (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 | | | |
| Lumbar radiculopathy | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 1 / 46 (2.17%) |
| 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 | | | |
| Vestibular disorder | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 | | | |
| Eye haemorrhage | | | |

| | | | |
|--|----------------|----------------|----------------|
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 51 (1.96%) | 0 / 46 (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 |
| Gastrointestinal disorders | | | |
| Enterovesical fistula | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 |
| Haematemesis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 |
| Melaena | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 |
| Abdominal pain | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 51 (1.96%) | 0 / 46 (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 |
| Abdominal pain upper | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 51 (0.00%) | 0 / 46 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 | | | |
| Nephrolithiasis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 colic | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 | | | |
| Osteoarthritis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 | | | |
| Abscess intestinal | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 |
| Diverticulitis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 |
| Viral infection | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 |
| Appendicitis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 1 / 46 (2.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometritis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 |
| Salpingo-oophoritis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 |
| Peritonsillar abscess | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (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 | Placebo/RNF 44 Mcg thrice Weekly (DB population) | RNF 44 Mcg Once Weekly (DB population) | RNF 44 Mcg thrice Weekly (DB population) |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 69 / 84 (82.14%) | 97 / 117 (82.91%) | 84 / 99 (84.85%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|------------------------|-------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 84 (0.00%) 0 | 0 / 117 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Aspartate aminotransferase increased alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 84 (0.00%) 0 | 0 / 117 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Blood creatine phosphokinase increased alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 84 (0.00%) 0 | 0 / 117 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Injury, poisoning and procedural complications Overdose alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 84 (0.00%) 0 | 0 / 117 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Vascular disorders Hypertension alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 5 / 84 (5.95%) 5 | 7 / 117 (5.98%) 7 | 1 / 99 (1.01%) 1 |
| Nervous system disorders Headache alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 11 / 84 (13.10%) 11 | 19 / 117 (16.24%) 19 | 16 / 99 (16.16%) 16 |
| Dizziness alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 84 (0.00%) 0 | 0 / 117 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Migraine alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 84 (0.00%) 0 | 0 / 117 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Insomnia | | | |

| | | | |
|--|------------------------|-------------------------|------------------------|
| alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 1 / 84 (1.19%) 1 | 7 / 117 (5.98%) 7 | 4 / 99 (4.04%) 4 |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 9 / 84 (10.71%) 9 | 2 / 117 (1.71%) 2 | 2 / 99 (2.02%) 2 |
| Lymphopenia | | | |
| alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 4 / 84 (4.76%) 4 | 1 / 117 (0.85%) 1 | 5 / 99 (5.05%) 5 |
| Neutropenia | | | |
| alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 8 / 84 (9.52%) 8 | 3 / 117 (2.56%) 3 | 5 / 99 (5.05%) 5 |
| General disorders and administration site conditions | | | |
| Influenza like illness | | | |
| alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 45 / 84 (53.57%) 45 | 39 / 117 (33.33%) 39 | 17 / 99 (17.17%) 17 |
| Injection site erythema | | | |
| alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 17 / 84 (20.24%) 17 | 6 / 117 (5.13%) 6 | 8 / 99 (8.08%) 8 |
| Chills | | | |
| alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 84 (0.00%) 0 | 0 / 117 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Fatigue | | | |
| alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 84 (0.00%) 0 | 0 / 117 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Ear and labyrinth disorders | | | |

| | | | |
|---|--|--|--|
| Vertigo alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 5 / 84 (5.95%) 5 | 1 / 117 (0.85%) 1 | 5 / 99 (5.05%) 5 |
| Gastrointestinal disorders Diarrhoea alternative assessment type: Systematic subjects affected / exposed occurrences (all) Toothache alternative assessment type: Systematic subjects affected / exposed occurrences (all) Dyspepsia alternative assessment type: Systematic subjects affected / exposed occurrences (all) Nausea alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 3 / 84 (3.57%) 3 5 / 84 (5.95%) 5 0 / 84 (0.00%) 0 0 / 84 (0.00%) 0 | 8 / 117 (6.84%) 8 4 / 117 (3.42%) 4 0 / 117 (0.00%) 0 0 / 117 (0.00%) 0 | 3 / 99 (3.03%) 3 4 / 99 (4.04%) 4 0 / 99 (0.00%) 0 0 / 99 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Oropharyngeal pain alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 84 (0.00%) 0 | 0 / 117 (0.00%) 0 | 0 / 99 (0.00%) 0 |
| Psychiatric disorders Anxiety alternative assessment type: Systematic subjects affected / exposed occurrences (all) Depression alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 3 / 84 (3.57%) 3 1 / 84 (1.19%) 1 | 7 / 117 (5.98%) 7 6 / 117 (5.13%) 6 | 4 / 99 (4.04%) 4 2 / 99 (2.02%) 2 |

| | | | |
|---|------------------|-------------------|----------------|
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| alternative assessment type: | | | |
| Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 0 / 99 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Back pain | | | |
| alternative assessment type: | | | |
| Systematic | | | |
| subjects affected / exposed | 5 / 84 (5.95%) | 7 / 117 (5.98%) | 6 / 99 (6.06%) |
| occurrences (all) | 5 | 7 | 6 |
| Pain in extremity | | | |
| alternative assessment type: | | | |
| Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 0 / 99 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| alternative assessment type: | | | |
| Systematic | | | |
| subjects affected / exposed | 3 / 84 (3.57%) | 5 / 117 (4.27%) | 6 / 99 (6.06%) |
| occurrences (all) | 3 | 5 | 6 |
| Cystitis | | | |
| alternative assessment type: | | | |
| Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 0 / 99 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| alternative assessment type: | | | |
| Systematic | | | |
| subjects affected / exposed | 3 / 84 (3.57%) | 8 / 117 (6.84%) | 7 / 99 (7.07%) |
| occurrences (all) | 3 | 8 | 7 |
| Nasopharyngitis | | | |
| alternative assessment type: | | | |
| Systematic | | | |
| subjects affected / exposed | 12 / 84 (14.29%) | 14 / 117 (11.97%) | 9 / 99 (9.09%) |
| occurrences (all) | 12 | 14 | 9 |
| Pharyngitis | | | |
| alternative assessment type: | | | |
| Systematic | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 117 (0.00%) | 0 / 99 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |

| | | | |
|--|------------------|------------------|------------------|
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 10 / 84 (11.90%) | 11 / 117 (9.40%) | 10 / 99 (10.10%) |
| occurrences (all) | 10 | 11 | 10 |
| Urinary tract infection | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 8 / 117 (6.84%) | 3 / 99 (3.03%) |
| occurrences (all) | 1 | 8 | 3 |

| Non-serious adverse events | Placebo/RNF 44 Mcg thrice Weekly/OL RNF 44 Mcg thrice weekly | RNF 44 Mcg Once Weekly /OL RNF 44 Mcg thrice Weekly | RNF 44 Mcg thrice Weekly/OL RNF 44 Mcg thrice Weekly |
|--|---|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 46 / 58 (79.31%) | 37 / 51 (72.55%) | 36 / 46 (78.26%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 2 / 51 (3.92%) | 3 / 46 (6.52%) |
| occurrences (all) | 1 | 2 | 3 |
| Aspartate aminotransferase increased | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 2 / 51 (3.92%) | 3 / 46 (6.52%) |
| occurrences (all) | 1 | 2 | 3 |
| Blood creatine phosphokinase increased | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | 1 / 51 (1.96%) | 0 / 46 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 8 / 51 (15.69%) | 1 / 46 (2.17%) |
| occurrences (all) | 2 | 8 | 1 |
| Vascular disorders | | | |
| Hypertension | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | 3 / 51 (5.88%) 3 | 1 / 46 (2.17%) 1 |
| Nervous system disorders | | | |
| Headache | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | 6 / 51 (11.76%) | 9 / 46 (19.57%) |
| occurrences (all) | 4 | 6 | 9 |
| Dizziness | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 1 / 51 (1.96%) | 3 / 46 (6.52%) |
| occurrences (all) | 1 | 1 | 3 |
| Migraine | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 3 / 51 (5.88%) | 0 / 46 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Insomnia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 1 / 51 (1.96%) | 4 / 46 (8.70%) |
| occurrences (all) | 2 | 1 | 4 |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 4 / 51 (7.84%) | 1 / 46 (2.17%) |
| occurrences (all) | 0 | 4 | 1 |
| Lymphopenia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutropenia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 4 / 51 (7.84%) | 1 / 46 (2.17%) |
| occurrences (all) | 0 | 4 | 1 |
| General disorders and administration site conditions | | | |
| Influenza like illness | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|--|------------------|------------------|------------------|
| subjects affected / exposed | 11 / 58 (18.97%) | 12 / 51 (23.53%) | 10 / 46 (21.74%) |
| occurrences (all) | 11 | 12 | 10 |
| Injection site erythema | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | 8 / 51 (15.69%) | 2 / 46 (4.35%) |
| occurrences (all) | 4 | 8 | 2 |
| Chills | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 3 / 51 (5.88%) | 2 / 46 (4.35%) |
| occurrences (all) | 0 | 3 | 2 |
| Fatigue | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 2 / 51 (3.92%) | 3 / 46 (6.52%) |
| occurrences (all) | 0 | 2 | 3 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 3 / 51 (5.88%) | 0 / 46 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Toothache | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 0 / 46 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspepsia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 51 (0.00%) | 3 / 46 (6.52%) |
| occurrences (all) | 0 | 0 | 3 |
| Nausea | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|---|---|--|
| subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | 3 / 51 (5.88%) 3 | 2 / 46 (4.35%) 2 |
| Respiratory, thoracic and mediastinal disorders Oropharyngeal pain alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 3 / 58 (5.17%) 3 | 2 / 51 (3.92%) 2 | 2 / 46 (4.35%) 2 |
| Psychiatric disorders Anxiety alternative assessment type: Systematic subjects affected / exposed occurrences (all) Depression alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 2 / 58 (3.45%) 2 0 / 58 (0.00%) 0 | 0 / 51 (0.00%) 0 0 / 51 (0.00%) 0 | 3 / 46 (6.52%) 3 0 / 46 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia alternative assessment type: Systematic subjects affected / exposed occurrences (all) Back pain alternative assessment type: Systematic subjects affected / exposed occurrences (all) Pain in extremity alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 2 / 58 (3.45%) 2 5 / 58 (8.62%) 5 4 / 58 (6.90%) 4 | 3 / 51 (5.88%) 3 2 / 51 (3.92%) 2 1 / 51 (1.96%) 1 | 0 / 46 (0.00%) 0 5 / 46 (10.87%) 5 1 / 46 (2.17%) 1 |
| Infections and infestations Bronchitis alternative assessment type: Systematic subjects affected / exposed occurrences (all) Cystitis | 4 / 58 (6.90%) 4 | 1 / 51 (1.96%) 1 | 2 / 46 (4.35%) 2 |

| | | | |
|--|-----------------|-----------------|-----------------|
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | 0 / 51 (0.00%) | 1 / 46 (2.17%) |
| occurrences (all) | 3 | 0 | 1 |
| Influenza | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | 2 / 51 (3.92%) | 3 / 46 (6.52%) |
| occurrences (all) | 4 | 2 | 3 |
| Nasopharyngitis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 6 / 58 (10.34%) | 7 / 51 (13.73%) | 4 / 46 (8.70%) |
| occurrences (all) | 6 | 7 | 4 |
| Pharyngitis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 0 / 51 (0.00%) | 4 / 46 (8.70%) |
| occurrences (all) | 2 | 0 | 4 |
| Upper respiratory tract infection | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 6 / 58 (10.34%) | 5 / 51 (9.80%) | 5 / 46 (10.87%) |
| occurrences (all) | 6 | 5 | 5 |
| Urinary tract infection | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 3 / 51 (5.88%) | 4 / 46 (8.70%) |
| occurrences (all) | 2 | 3 | 4 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|--|
| 15 July 2009 | The purpose of this amendment was: <ul style="list-style-type: none">- To ensure that AEs, concomitant medications and procedures that occurred prior to the baseline of Trial 28981 (i.e. within the 24 month period of Trial 27025) were collected only once -- i.e., in Trial 27025 rather than in Trial 28981.- Change of the visit window from ± 21 days to ± 7 days- Reduction of the number of visits required by subjects (i.e., visits at Months 25, 27, 33, 39, 45, 51 and 57 could be eliminated for some subjects) |
| 11 July 2011 | This amendment was substantial, global except in France. The purpose of this amendment was: <ul style="list-style-type: none">- Introduction of new assessments (years of education and vocational status) at Month 60- Clarification of operational aspects of the trial related to blood sampling- To include a provision for a possible switch of subjects from ow dosing to tiw dosing upon availability of the Month 36 results |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported