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 administrated 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 administrated 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 administrated 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
Unspecifed	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 administrated 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 administrated 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 administrated 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 402subjects 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 administrated 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 administrated 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 administrated 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	31	31.4	31.8
standard deviation	± 8.2	± 8.2	± 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 administrated 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 administrated 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 administrated 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 administrated 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 administrated 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 administrated 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	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 administrated 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 administrated 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 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 administrated 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 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	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	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 administrated 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 administrated 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 administrated 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			
Appendicectomy			
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	0 / 84 (0.00%)	0 / 117 (0.00%)	0 / 99 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 84 (0.00%)	0 / 117 (0.00%)	0 / 99 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 84 (0.00%)	0 / 117 (0.00%)	0 / 99 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Overdose			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 84 (0.00%)	0 / 117 (0.00%)	0 / 99 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 84 (5.95%)	7 / 117 (5.98%)	1 / 99 (1.01%)
occurrences (all)	5	7	1
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	11 / 84 (13.10%)	19 / 117 (16.24%)	16 / 99 (16.16%)
occurrences (all)	11	19	16
Dizziness			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 84 (0.00%)	0 / 117 (0.00%)	0 / 99 (0.00%)
occurrences (all)	0	0	0
Migraine			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 84 (0.00%)	0 / 117 (0.00%)	0 / 99 (0.00%)
occurrences (all)	0	0	0
Insomnia			

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

Vertigo			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 84 (5.95%)	1 / 117 (0.85%)	5 / 99 (5.05%)
occurrences (all)	5	1	5
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 84 (3.57%)	8 / 117 (6.84%)	3 / 99 (3.03%)
occurrences (all)	3	8	3
Toothache			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 84 (5.95%)	4 / 117 (3.42%)	4 / 99 (4.04%)
occurrences (all)	5	4	4
Dyspepsia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 84 (0.00%)	0 / 117 (0.00%)	0 / 99 (0.00%)
occurrences (all)	0	0	0
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 84 (0.00%)	0 / 117 (0.00%)	0 / 99 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 84 (0.00%)	0 / 117 (0.00%)	0 / 99 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 84 (3.57%)	7 / 117 (5.98%)	4 / 99 (4.04%)
occurrences (all)	3	7	4
Depression			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 84 (1.19%)	6 / 117 (5.13%)	2 / 99 (2.02%)
occurrences (all)	1	6	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	0 / 58 (0.00%)	3 / 51 (5.88%)	1 / 46 (2.17%)
occurrences (all)	0	3	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	0 / 58 (0.00%)	3 / 51 (5.88%)	2 / 46 (4.35%)
occurrences (all)	0	3	2
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 58 (5.17%)	2 / 51 (3.92%)	2 / 46 (4.35%)
occurrences (all)	3	2	2
Psychiatric disorders			
Anxiety			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 58 (3.45%)	0 / 51 (0.00%)	3 / 46 (6.52%)
occurrences (all)	2	0	3
Depression			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 58 (0.00%)	0 / 51 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 58 (3.45%)	3 / 51 (5.88%)	0 / 46 (0.00%)
occurrences (all)	2	3	0
Back pain			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 58 (8.62%)	2 / 51 (3.92%)	5 / 46 (10.87%)
occurrences (all)	5	2	5
Pain in extremity			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 58 (6.90%)	1 / 51 (1.96%)	1 / 46 (2.17%)
occurrences (all)	4	1	1
Infections and infestations			
Bronchitis			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 58 (6.90%)	1 / 51 (1.96%)	2 / 46 (4.35%)
occurrences (all)	4	1	2
Cystitis			

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: - 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: - 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