ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
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ClinicalTrials.gov ID: NCT00404352

Study Identification

Unique Protocol ID:	IMP27025
Brief Title:	REbif FLEXible Dosing in Early Multiple Sclerosis (MS) (REFLEX)
Official Title:	A Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter Clinical Trial of Rebif New Formulation (44 Microgram [mcg] Three Times Weekly [Tiw] and 44 mcg Once Weekly [ow]) in Subjects at High Risk of Converting to Multiple Sclerosis (REFLEX)
Secondary IDs:	2006-002982-38 [EudraCT Number]

Study Status

Record Verification:	December 2013
Overall Status:	Completed
Study Start:	November 2006
Primary Completion:	August 2010 [Actual]
Study Completion:	July 2011 [Actual]

Sponsor/Collaborators

Sponsor:	Merck KGaA
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes

Applicable Trial?:	Section 801 Clinical Trial? No Delayed Posting? No
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 5932 Board Name: Committee on Ethics under Federal Body for Quality Control of Medical Products Board Affiliation: Independent Phone: +7 (495) 625 43 86 Email:
Data Monitoring?:	Yes
Plan to Share Data?:	
Oversight Authorities:	Argentina: Administracion Nacional de Medicamentos, Alimentos y Tecnologia Medica Australia: Department of Health and Ageing Therapeutic Goods Administration Australia: Human Research Ethics Committee Austria: Agency for Health and Food Safety Austria: Ethikkommission Belgium: The Federal Public Service (FPS) Health, Food Chain Safety and Environment Bulgaria: Bulgarian Drug Agency Bulgaria: Ministry of Health Canada: Canadian Institutes of Health Research Croatia: Ministry of Health and Social Care Czech Republic: Ethics Committee Czech Republic: State Institute for Drug Control Denmark: Danish Dataprotection Agency Denmark: Danish Medicines Agency Denmark: Ethics Committee Estonia: The State Agency of Medicine Finland: Ethics Committee Finland: Finnish Medicines Agency France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis) France: Ministry of Health France: National Consultative Ethics Committee for Health and Life Sciences Germany: Federal Institute for Drugs and Medical Devices Germany: Ministry of Health Greece: Ministry of Health and Welfare Hungary: National Institute of Pharmacy Israel: Ministry of Health Italy: Ethics Committee Latvia: State Agency of Medicines Lithuania: Bioethics Committee Lithuania: State Medicine Control Agency - Ministry of Health Macedonia: Ethics Committee

Morocco: Ministry of Public Health
Netherlands: The Central Committee on Research Involving Human Subjects (CCMO)
Poland: Ministry of Health
Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Romania: Ministry of Public Health
Romania: National Medicines Agency
Russia: Ethics Committee
Russia: Ministry of Health of the Russian Federation
Serbia and Montenegro: Agency for Drugs and Medicinal Devices
Serbia: Ethics Committee
Slovakia: State Institute for Drug Control
Spain: Comité Ético de Investigación Clínica
Spain: Ministry of Health
Switzerland: Ethikkommission
Switzerland: Swissmedic
Turkey: Ethics Committee
Turkey: Ministry of Health

Study Description

Brief Summary: The study is a 24 months randomized, double-blind, Placebo-controlled, multi-center clinical trial with an optional 12 months open label extension.

The primary objective of the study is to evaluate the effect of fetal bovine serum [FBS]-free/human serum albumin [HSA]-free formulation of Interferon [IFN] beta-1a (RNF) 44 microgram (three times weekly and once weekly) versus placebo on the time to conversion to McDonald multiple sclerosis (MS) criteria (2005) in subjects with a first clinical demyelinating event at high risk of converting to MS.

The main secondary objective of study is to evaluate the effect of RNF 44 microgram (three times weekly and once weekly) versus placebo on the "Time to conversion to clinically definite MS (CDMS)" in subjects with a first clinical demyelinating event at high risk of converting to MS.

At the end of 24 month double-blind core REFLEX trial, subjects who will not convert to CDMS and decide to receive open-label (OL) treatment will be enrolled into an open-label, 12 month extension period to evaluate the effect of RNF 44 mcg three times weekly treatment on the time to conversion to McDonald MS and time to conversion to CDMS.

Detailed Description:

Conditions

Conditions: Multiple Sclerosis

Keywords: Rebif New Formulation
Clinical Isolated Syndrome
Multiple Sclerosis

Study Design

Study Type:	Interventional
Primary Purpose:	Prevention
Study Phase:	Phase 3
Intervention Model:	Parallel Assignment
Number of Arms:	3
Masking:	Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Allocation:	Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	517 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Active Comparator: RNF 44 mcg three times weekly	Drug: RNF Single dose of RNF 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 24 months, or 36 months for patients enrolled in the OL extension. Other Names: • Rebif Drug: RNF Single dose of RNF 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 24 months. Other Names: • Rebif
Active Comparator: RNF 44 mcg once weekly and placebo twice weekly for blinding	Drug: RNF Single dose of RNF 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 24 months, or 36 months for patients enrolled in the OL extension. Other Names: • Rebif Drug: RNF

Arms	Assigned Interventions
	Single dose of RNF 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 24 months. Other Names: • Rebif Drug: Placebo Placebo was supplied as a transparent, sterile solution for injection in pre-filled syringes matching the RNF pre-filled syringes, each containing 0.5 mL.
Placebo Comparator: Placebo three times weekly	Drug: Placebo Placebo was supplied as a transparent, sterile solution for injection in pre-filled syringes matching the RNF pre-filled syringes, each containing 0.5 mL.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age: 50 Years

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Single, first clinical event suggestive of MS within 60 days prior to study Day 1, which is the day of randomization (clock starts 24 hours after onset). The event must be a new neurological abnormality present for at least 24 hours, either mono- or polysymptomatic, other than a paresthesia, vegetative or cerebral dysfunction
- At least two clinically silent lesions on the T2-weighted MRI scan, with a size of at least 3 millimeter (mm), at least one of which is ovoid or periventricular or infratentorial
- EDSS 0 - 5.0 at least one time point during the screening period before start of treatment
- 18 and 50 years old, inclusive
- Willing to follow study procedures
- Written informed consent
- If female, subject must:
  - be neither pregnant nor breast-feeding nor attempting to conceive
  - use a highly effective method of contraception. A highly effective method of contraception is defined as those which result in a low failure rate (that is [i.e.] less than 1 percent [%] per year) when used consistently and correctly such

as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomised partner

Exclusion Criteria:

- Diagnosis of MS (per McDonald criteria 2005)
- Any other disease that could better explain the subject's signs and symptoms
- Complete transverse myelitis or bilateral optic neuritis
- Subject uses or has used any other approved MS disease-modifying drug (DMD)
- Any investigational drug or undergone an experimental procedure within 12 weeks prior to study Day 1
- Oral or systemic corticosteroids or adrenocorticotropic hormone (ACTH) within 30 days prior to study Day 1
- Total bilirubin greater than 2.5 times upper limit of normal (ULN)
- Subject has total aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or alkaline phosphatase (ALP) greater than 2.5 times the ULN
- Inadequate bone marrow reserve, defined as a total white blood cell count less than 3.0 x 109 per liter (/L), platelet count less than 75 x 109/L, hemoglobin less than 100 gram per liter (g/L)
- Current autoimmune disease
- Major medical or psychiatric illness (including history of or current severe depressive disorders and/or suicidal ideation) that in the opinion of the investigator creates undue risk to the subject or could affect compliance with the study protocol
- History of seizures not adequately controlled by treatment
- Cardiac disease, such as angina, congestive heart failure or arrhythmia
- Known allergy to IFN-beta or the excipient(s) of the study medication
- Any condition that could interfere with the MRI evaluation;
- Known allergy to gadolinium-diethylene triamine pentaacetic acid (DTPA)
- Previously participated in this study
- Participated in any clinical trial within the past 6 months
- Any immunomodulatory or immunosuppressive therapy at any time prior to enrollment, including, but not limited to, the following products: any IFN, glatiramer acetate (Copolymer I), cyclophosphamide, cyclosporine, methotrexate, linomide, azathioprine, mitoxantrone, teriflunomide, laquinimod, cladribine, total lymphoid irradiation, anti-lymphocyte monoclonal antibody treatment (e.g. natalizumab, alemtuzumab/Campath, anti-cluster of differentiation 4 [CD4]), intravenous, immunoglobulins (Igs), cytokines or anti-cytokine therapy
- Any experimental MS treatment prior to trial entry, including, but not limited to, any statins (if given to prevent MS) and pentoxyfylline
- History of alcohol or drug abuse
- Intolerance or any contraindication to both paracetamol (acetaminophen) and ibuprofen
- Inability to administer subcutaneous injections either by self or by caregiver
- Moderate to severe renal impairment

Contacts/Locations

Study Officials: Bettina M. Stubinski, MD
Study Director
Merck Serono S.A., Geneva, an affiliate of Merck KGaA, Darmstadt, Germany

Locations: Australia
Research Site
Sydney, Australia

Canada
Research Site
Ontario, Canada

Germany
Research Site
Munich, Germany

Spain
Research Site
Madrid, Spain

Finland
Research Site
Vantaa, Finland

France
Research Site
Paris, France

Greece
Research Site
Athens, Greece

Israel
Research Site
Ness Ziona, Israel

Italy
Research Site
Roma, Italy

Turkey
Research Site
Istanbul, Turkey

Argentina
Research Site
Mendoza, Argentina

Austria
Research Site

Innsbruck, Austria

Research Site
Graz, Austria

Belgium
Research Site
B-Leuven, Belgium

Research Site
Brugge, Belgium

Bulgaria
Research Site
Varna, Bulgaria

Research Site
Sofia, Bulgaria

Research Site
Shumen, Bulgaria

Research Site
Rousse, Bulgaria

Research Site
Pleven, Bulgaria

Canada
Research Site
Montreal, Quebec, Canada

Research Site
Victoria British Columbia, Canada

Croatia
Research Site
Zagreb, Croatia

Research Site
Karlovac, Croatia

Research Site
Split, Croatia

Research Site

Rijeka, Croatia

Research Site
Osijek, Croatia

Czech Republic
Research Site
Prague, Czech Republic

Research Site
Olomouc, Czech Republic

Research Site
Hradec Kralove, Czech Republic

Estonia
Research Site
Tallinn, Estonia

Research Site
Tartu, Estonia

Finland
Research Site
OYS, Finland

France
Research Site
Poissy Cedex, France

Germany
Research Site
Hannover, Germany

Research Site
Henningsdorf, Germany

Israel
Research Site
Tel-Hashomer, Israel

Research Site
Safed, Israel

Italy
Research Site

Padova, Italy

Research Site
Catania, Italy

Research Site
Milano, Italy

Latvia
Research Site
Riga, Latvia

Lebanon
Research Site
Beirut, Lebanon

Morocco
Research Site
Rabat, Morocco

Poland
Research Site
Warsaw, Poland

Research Site
Wroclaw, Poland

Research Site
Bialystok, Poland

Research Site
Lodz, Poland

Portugal
Research Site
Lisboa, Portugal

Romania
Research Site
Bucharest, Romania

Research Site
Targu-Mures, Romania

Research Site
Iasi, Romania

Research Site
Bucharest, Romania

Research Site
Timisoara, Romania

Russian Federation
Research Site
Nizhny Novgorod, Russian Federation

Research Site
Moscow, Russian Federation

Research Site
Ekaterinburg, Russian Federation

Research Site
Saint-Petersburg, Russian Federation

Research Site
Saratov, Russian Federation

Research Site
Novosibirsk, Russian Federation

Research Site
Samara, Russian Federation

Saudi Arabia
Research Site
Riyadh, Saudi Arabia

Serbia
Research Site
Belgrade, Serbia

Research Site
Nis, Serbia

Slovakia
Research Site
Presov, Slovakia

Spain
Research Site
Barcelona, Spain

Research Site
Sevilla, Spain

Research Site
Bilbao, Spain

References

Citations:

Links: URL: http://www.mslifelines.com
Description Full FDA approved prescribing information can be found here

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	The participants were recruited in 78 centers across 28 countries for REFLEX study. REFLEX 12 months open label extension (OLE) was conducted at 11 active centers in 9 countries.

Reporting Groups

	Description
RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)	Single dose of fetal bovine serum [FBS]-free/human serum albumin [HSA]-free formulation of interferon [IFN]-beta-1a (RNF) injection 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 24 months or until conversion to clinically definite multiple sclerosis (CDMS) whichever occurs first.
RNF 44 Mcg Once Weekly (DB Population)	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 finally 44 mcg until 24 months or until conversion to CDMS whichever occurs first.
Placebo (DB Population)	Single dose of matching placebo administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 24 months or until conversion to CDMS whichever occurs first.
RNF 44 Mcg Three Times Weekly/OL RNF 44 Mcg Three Times Weekly	After having converted to CDMS, participants 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 24 months.

	Description
RNF 44 Mcg Once Weekly/OL RNF 44 Mcg Three Times Weekly	After having converted to CDMS, participants 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 24 months.
Placebo/OL RNF 44 Mcg Three Times Weekly	After having converted to CDMS, participants 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 24 months.
RNF 44Mcg Three Times Weekly/ RNF 44Mcg Three Times Weekly(OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year open label extension (OLE). Participants who had received RNF three times a week in the core REFLEX trial, were re-titrated with a single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 36 months in this 12 months open label extension.
RNF 44 Mcg Once Weekly/RNF 44 Mcg Three Times Weekly (OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year OLE. Participants who had received RNF once weekly in the core REFLEX trial were re-titrated with a single dose of RNF injection 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 in this 12 months open label extension.
Placebo/RNF 44 Mcg Three Times Weekly (OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year OLE. Participants who had received placebo in the core REFLEX trial were re-titrated with a single dose of RNF injection 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 in this 12 months open label extension.

Double Blind (up to 24 Month)

	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)	RNF 44 Mcg Once Weekly (DB Population)	Placebo (DB Population)	RNF 44 Mcg Three Times Weekly/OL RNF 44 Mcg Three Times Weekly	RNF 44 Mcg Once Weekly/OL RNF 44 Mcg Three Times Weekly	Placebo/OL RNF 44 Mcg Three Times Weekly
Started	171	175	171	0	0	0
Treated	171	173	171	0	0	0
Completed	119	128	92	0	0	0
Not Completed	52	47	79	0	0	0
Adverse Event	5	4	6	0	0	0
Pregnancy	0	0	2	0	0	0
Death	0	0	1	0	0	0

	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)	RNF 44 Mcg Once Weekly (DB Population)	Placebo (DB Population)	RNF 44 Mcg Three Times Weekly/OL RNF 44 Mcg Three Times Weekly	RNF 44 Mcg Once Weekly/OL RNF 44 Mcg Three Times Weekly	Placebo/OL RNF 44 Mcg Three Times Weekly
Lost to Follow-up	1	2	1	0	0	0
Withdrawal by Subject	11	8	7	0	0	0
Disease progression	3	0	2	0	0	0
Poor compliance	1	0	0	0	0	0
Switched to open label phase	31	30	59	0	0	0
Randomized but not treated	0	2	0	0	0	0
Physician Decision	0	0	1	0	0	0
Unspecified	0	1	0	0	0	0

	RNF 44Mcg Three Times Weekly/ RNF 44Mcg Three Times Weekly(OLE)	RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)	Placebo/ RNF 44 Mcg Three Times Weekly (OLE)
Started	0	0	0
Treated	0	0	0
Completed	0	0	0
Not Completed	0	0	0
Adverse Event	0	0	0
Pregnancy	0	0	0
Death	0	0	0
Lost to Follow-up	0	0	0
Withdrawal by Subject	0	0	0
Disease progression	0	0	0

	RNF 44Mcg Three Times Weekly/ RNF 44Mcg Three Times Weekly(OLE)	RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)	Placebo/ RNF 44 Mcg Three Times Weekly (OLE)
Poor compliance	0	0	0
Switched to open label phase	0	0	0
Randomized but not treated	0	0	0
Physician Decision	0	0	0
Unspecified	0	0	0

Open Label (up to 24 Month)

	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)	RNF 44 Mcg Once Weekly (DB Population)	Placebo (DB Population)	RNF 44 Mcg Three Times Weekly/OL RNF 44 Mcg Three Times Weekly	RNF 44 Mcg Once Weekly/OL RNF 44 Mcg Three Times Weekly	Placebo/OL RNF 44 Mcg Three Times Weekly
Started	0	0	0	31 [1]	30 [2]	59 [3]
Completed	0	0	0	28	28	52
Not Completed	0	0	0	3	2	7
Adverse Event	0	0	0	2	1	1
Pregnancy	0	0	0	0	0	1
Lost to Follow-up	0	0	0	0	1	0
Withdrawal by Subject	0	0	0	0	0	5
Disease progression	0	0	0	1	0	0

[1] From DB period, 31 participants converted to CDMS and switched to OL period in this study
[2] From DB period, 30 participants converted to CDMS and switched to OL period in this study
[3] From DB period, 59 participants converted to CDMS and switched to OL period in this study

	RNF 44Mcg Three Times Weekly/ RNF 44Mcg Three Times Weekly(OLE)	RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)	Placebo/ RNF 44 Mcg Three Times Weekly (OLE)
Started	0	0	0
Completed	0	0	0
Not Completed	0	0	0
Adverse Event	0	0	0
Pregnancy	0	0	0
Lost to Follow-up	0	0	0
Withdrawal by Subject	0	0	0
Disease progression	0	0	0

Open Label Extension (up to 36 Months)

	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)	RNF 44 Mcg Once Weekly (DB Population)	Placebo (DB Population)	RNF 44 Mcg Three Times Weekly/OL RNF 44 Mcg Three Times Weekly	RNF 44 Mcg Once Weekly/OL RNF 44 Mcg Three Times Weekly	Placebo/OL RNF 44 Mcg Three Times Weekly
Started	0	0	0	0	0	0
Completed	0	0	0	0	0	0
Not Completed	0	0	0	0	0	0
Adverse Event	0	0	0	0	0	0
unspecified	0	0	0	0	0	0

	RNF 44Mcg Three Times Weekly/ RNF 44Mcg Three Times Weekly(OLE)	RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)	Placebo/ RNF 44 Mcg Three Times Weekly (OLE)
Started	4 [1]	5 [2]	11 [3]
Completed	3	4	9
Not Completed	1	1	2
Adverse Event	1	1	0
unspecified	0	0	2

[1] 4 participants who did not convert to CDMS in 24 months and gave consent to enroll in OLE period
[2] 5 participants who did not convert to CDMS in 24 months and gave consent to enroll in OLE period
[3] 11 participants who did not convert to CDMS in 24 months and gave consent to enroll in OLE period

Baseline Characteristics

Reporting Groups

	Description
RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)	Single dose of fetal bovine serum [FBS]-free/human serum albumin [HSA]-free formulation of interferon [IFN]-beta-1a (RNF) injection 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 24 months or until conversion to clinically definite multiple sclerosis (CDMS) whichever occurs first.
RNF 44 Mcg Once Weekly (DB Population)	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 finally 44 mcg until 24 months or until conversion to CDMS whichever occurs first.
Placebo (DB Population)	Single dose of matching placebo administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 24 months or until conversion to CDMS whichever occurs first.

Baseline Measures

	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)	RNF 44 Mcg Once Weekly (DB Population)	Placebo (DB Population)	Total
Number of Participants	171	175	171	517
Age, Continuous [units: years] Mean (Standard Deviation)	30.6 (8.5)	30.7 (8.1)	30.9 (7.9)	30.7 (8.2)
Age, Customized [units: participants]				
Less than 30 years	86	86	87	259
Greater than or equal to 30 years	85	89	84	258
Gender, Male/Female [units: participants]				
Female	114	106	112	332
Male	57	69	59	185
Race/Ethnicity, Customized [units: participants]				
Asian	0	0	0	0
Black	0	1	0	1
White	171	174	171	516
Other	0	0	0	0

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Time to Conversion to Multiple Sclerosis (MS) According to the McDonald Criteria (2005)
Measure Description	The McDonald criteria use dissemination in time and space established by magnetic resonance image (MRI) findings to provide a clinical diagnosis for MS. Dissemination in time is established by a new time constant 2 (T2) or gadolinium-enhancing (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.
Time Frame	Various time points from randomization up to 24 months
Safety Issue?	No

Analysis Population Description

Intent-to-treat (ITT) population included all participants who were randomized to the assigned study treatment.

Reporting Groups

	Description
RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)	Single dose of fetal bovine serum [FBS]-free/human serum albumin [HSA]-free formulation of interferon [IFN]-beta-1a (RNF) injection 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 24 months or until conversion to clinically definite multiple sclerosis (CDMS) whichever occurs first.
RNF 44 Mcg Once Weekly (DB Population)	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 finally 44 mcg until 24 months or until conversion to CDMS whichever occurs first.
Placebo (DB Population)	Single dose of matching placebo administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 24 months or until conversion to CDMS whichever occurs first.

Measured Values

	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)	RNF 44 Mcg Once Weekly (DB Population)	Placebo (DB Population)
Number of Participants Analyzed	171	175	171
Time to Conversion to Multiple Sclerosis (MS) According to the McDonald Criteria (2005) [units: days] Median (95% Confidence Interval)	310 (183 to 488)	182 (107 to 270)	97 (93 to 101)

Statistical Analysis 1 for Time to Conversion to Multiple Sclerosis (MS) According to the McDonald Criteria (2005)

Statistical Analysis Overview	Comparison Groups	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population), Placebo (DB Population)
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]

	Method	Log Rank
	Comments	Log-rank test was stratified for controlling randomization stratification factors.

Statistical Analysis 2 for Time to Conversion to Multiple Sclerosis (MS) According to the McDonald Criteria (2005)

Statistical Analysis Overview	Comparison Groups	RNF 44 Mcg Once Weekly (DB Population), Placebo (DB Population)
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.008
	Comments	[Not specified]
	Method	Log Rank
	Comments	Log-rank test was stratified for controlling randomization stratification factors.

Statistical Analysis 3 for Time to Conversion to Multiple Sclerosis (MS) According to the McDonald Criteria (2005)

Statistical Analysis Overview	Comparison Groups	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population), RNF 44 Mcg Once Weekly (DB Population)
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.009
	Comments	[Not specified]
	Method	Log Rank
	Comments	Log-rank test was stratified for controlling randomization stratification factors.

2. Primary Outcome Measure:

Measure Title	Time to Conversion to Multiple Sclerosis (MS) According to the McDonald Criteria (2005)

Measure 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 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.
Time Frame	Various time points from randomization up to 36 months
Safety Issue?	No

Analysis Population Description

Open label (OL) ITT population included all participants who were randomized at baseline in core REFLEX trial and entered the 12 months OLE period.

Reporting Groups

	Description
RNF 44Mcg Three Times Weekly/ RNF 44Mcg Three Times Weekly(OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year open label extension (OLE). Participants who had received RNF three times a week in the core REFLEX trial, were re-titrated with a single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 36 months in this 12 months open label extension.
RNF 44 Mcg Once Weekly/RNF 44 Mcg Three Times Weekly (OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year OLE. Participants who had received RNF once weekly in the core REFLEX trial were re-titrated with a single dose of RNF injection 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 in this 12 months open label extension.
Placebo/RNF 44 Mcg Three Times Weekly (OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year OLE. Participants who had received placebo in the core REFLEX trial were re-titrated with a single dose of RNF injection 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 in this 12 months open label extension.

Measured Values

	RNF 44Mcg Three Times Weekly/RNF 44Mcg Three Times Weekly(OLE)	RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)	Placebo/RNF 44 Mcg Three Times Weekly (OLE)
Number of Participants Analyzed	4	5	11
Time to Conversion to Multiple Sclerosis (MS) According to the McDonald Criteria (2005) [units: days] Median (95% Confidence Interval)	NA (NA to NA) [1]	NA (NA to NA) [1]	NA (NA to NA) [1]

[1] Data could not be analyzed as none of the participants converted to MS according to the McDonald Criteria in the 12 month OLE period.

3. Secondary Outcome Measure:

Measure Title	Time to Conversion to Clinically Definite Multiple Sclerosis (CDMS) Defined by Either a Second Attack or a 3-Month Sustained Increase (Greater Than or Equal to 1.5 Points) in the Expanded Disability Status Scale (EDSS) Score
Measure Description	CDMS was defined by the occurrence of a second exacerbation or relapse over 24 months in participants who presented with first clinical demyelinating event (FCDE) accompanied by an abnormal MRI scan. EDSS assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to MS) was calculated.
Time Frame	Various time points from randomization up to 24 months
Safety Issue?	No

Analysis Population Description

ITT population included all participants who were randomized to the assigned study treatment.

Reporting Groups

	Description
RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)	Single dose of fetal bovine serum [FBS]-free/human serum albumin [HSA]-free formulation of interferon [IFN]-beta-1a (RNF) injection 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 24 months or until conversion to clinically definite multiple sclerosis (CDMS) whichever occurs first.
RNF 44 Mcg Once Weekly (DB Population)	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 finally 44 mcg until 24 months or until conversion to CDMS whichever occurs first.
Placebo (DB Population)	Single dose of matching placebo administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 24 months or until conversion to CDMS whichever occurs first.

Measured Values

	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)	RNF 44 Mcg Once Weekly (DB Population)	Placebo (DB Population)
Number of Participants Analyzed	171	175	171
Time to Conversion to Clinically Definite Multiple Sclerosis (CDMS) Defined by Either a Second Attack or a 3-Month Sustained Increase (Greater Than or Equal to 1.5 Points) in the Expanded Disability Status Scale (EDSS) Score [units: days]	NA (NA to NA) [1]	NA (NA to NA) [1]	NA (NA to NA) [1]

	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)	RNF 44 Mcg Once Weekly (DB Population)	Placebo (DB Population)
Median (95% Confidence Interval)			

[1] Non-estimable: Insufficient participants reached the median percentile to calculate the upper and lower limits of confidence interval.

Statistical Analysis 1 for Time to Conversion to Clinically Definite Multiple Sclerosis (CDMS) Defined by Either a Second Attack or a 3-Month Sustained Increase (Greater Than or Equal to 1.5 Points) in the Expanded Disability Status Scale (EDSS) Score

Statistical Analysis Overview	Comparison Groups	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population), Placebo (DB Population)
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	Log Rank
	Comments	Log-rank test was stratified for controlling randomization stratification factors.

Statistical Analysis 2 for Time to Conversion to Clinically Definite Multiple Sclerosis (CDMS) Defined by Either a Second Attack or a 3-Month Sustained Increase (Greater Than or Equal to 1.5 Points) in the Expanded Disability Status Scale (EDSS) Score

Statistical Analysis Overview	Comparison Groups	RNF 44 Mcg Once Weekly (DB Population), Placebo (DB Population)
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.002
	Comments	[Not specified]
	Method	Log Rank
	Comments	Log-rank test was stratified for controlling randomization stratification factors.

Statistical Analysis 3 for Time to Conversion to Clinically Definite Multiple Sclerosis (CDMS) Defined by Either a Second Attack or a 3-Month Sustained Increase (Greater Than or Equal to 1.5 Points) in the Expanded Disability Status Scale (EDSS) Score

Statistical Analysis Overview	Comparison Groups	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population), RNF 44 Mcg Once Weekly (DB Population)
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.774
	Comments	[Not specified]
	Method	Log Rank
	Comments	Log-rank test was stratified for controlling randomization stratification factors.

4. Secondary Outcome Measure:

Measure Title	Time to Conversion to Clinically Definite Multiple Sclerosis (CDMS) Defined by Either a Second Attack or a 3-Month Sustained Increase (Greater Than or Equal to 1.5 Points) in the Expanded Disability Status Scale (EDSS) Score
Measure Description	CDMS was defined by the occurrence of a second exacerbation or relapse over 36 months in participants who presented with FCDE accompanied by an abnormal MRI scan. EDSS assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to MS) was calculated.
Time Frame	Various time points from randomization up to 36 months
Safety Issue?	No

Analysis Population Description

OL ITT population included all participants who were randomized at baseline in core REFLEX trial and entered the 12 months OLE period.

Reporting Groups

	Description
RNF 44Mcg Three Times Weekly/ RNF 44Mcg Three Times Weekly(OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year open label extension (OLE). Participants who had received RNF three times a week in the core REFLEX trial, were re-titrated with a single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 36 months in this 12 months open label extension.

	Description
RNF 44 Mcg Once Weekly/RNF 44 Mcg Three Times Weekly (OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year OLE. Participants who had received RNF once weekly in the core REFLEX trial were re-titrated with a single dose of RNF injection 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 in this 12 months open label extension.
Placebo/RNF 44 Mcg Three Times Weekly (OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year OLE. Participants who had received placebo in the core REFLEX trial were re-titrated with a single dose of RNF injection 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 in this 12 months open label extension.

Measured Values

	RNF 44Mcg Three Times Weekly/RNF 44Mcg Three Times Weekly(OLE)	RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)	Placebo/RNF 44 Mcg Three Times Weekly (OLE)
Number of Participants Analyzed	4	5	11
Time to Conversion to Clinically Definite Multiple Sclerosis (CDMS) Defined by Either a Second Attack or a 3-Month Sustained Increase (Greater Than or Equal to 1.5 Points) in the Expanded Disability Status Scale (EDSS) Score [units: days] Median (95% Confidence Interval)	NA (NA to NA) [1]	NA (NA to NA) [1]	NA (NA to NA) [1]

[1] Insufficient participants reached the median percentile to calculate the upper and lower limits of confidence interval.

5. Secondary Outcome Measure:

Measure Title	Mean Number of Combined Unique Active (CUA) Lesions, New Time Constant 2 (T2) Lesions, Gadolinium Enhanced (Gd+) Lesions and New Time Constant 1 (T1) Hypointense Lesions Per Participant Per Scan
Measure Description	Number of CUA lesions, new T2 lesions, Gd+ lesions and new T1 hypointense lesions were measured by using MRI scans.
Time Frame	Month 24 up to Month 36
Safety Issue?	No

Analysis Population Description

OL ITT population included all participants who were randomized at baseline in core REFLEX trial and entered the 12 months OLE period. "n" signifies those participants who were evaluated for this measure at the specified time point for each arm group respectively.

Reporting Groups

	Description
RNF 44Mcg Three Times Weekly/ RNF 44Mcg Three Times Weekly(OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year open label extension (OLE). Participants who had received RNF three times a week in the core REFLEX trial, were re-titrated with a single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 36 months in this 12 months open label extension.
RNF 44 Mcg Once Weekly/RNF 44 Mcg Three Times Weekly (OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year OLE. Participants who had received RNF once weekly in the core REFLEX trial were re-titrated with a single dose of RNF injection 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 in this 12 months open label extension.
Placebo/RNF 44 Mcg Three Times Weekly (OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year OLE. Participants who had received placebo in the core REFLEX trial were re-titrated with a single dose of RNF injection 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 in this 12 months open label extension.

Measured Values

	RNF 44Mcg Three Times Weekly/RNF 44Mcg Three Times Weekly(OLE)	RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)	Placebo/RNF 44 Mcg Three Times Weekly (OLE)
Number of Participants Analyzed	4	5	11
Mean Number of Combined Unique Active (CUA) Lesions, New Time Constant 2 (T2) Lesions, Gadolinium Enhanced (Gd+) Lesions and New Time Constant 1 (T1) Hypointense Lesions Per Participant Per Scan [units: lesions] Mean (Standard Deviation)			
CUA lesions (n=3,5,9)	0.33 (0.58)	0.00 (0.00)	1.56 (2.93)
New T2 lesions (n=3,5,9)	0.17 (0.29)	0.00 (0.00)	0.94 (1.61)
New Gd+ lesions (n=3,5,9)	0.17 (0.29)	0.00 (0.00)	0.56 (1.21)
New T1 Hypointense lesions (n=3,5,9)	0.17 (0.29)	0.00 (0.00)	0.56 (0.88)

6. Secondary Outcome Measure:

Measure Title	Change From Baseline in Time Constant 2 (T2) Lesion Volume , Time Constant 1 (T1) Hypointense Lesion Volume and Gadolinium Enhanced (Gd+) Lesion Volume at Month 36
Measure Description	Change from baseline in lesion volume was measured by using MRI scans for T2 lesions, T1 hypointense lesions and (Gd+) lesions.
Time Frame	Baseline, Month 36
Safety Issue?	No

Analysis Population Description

OL ITT population included all participants who were randomized at baseline in core REFLEX trial and entered the 12 months OLE period. "n" signifies those participants who were evaluated for this measure at the specified time point for each arm group respectively.

Reporting Groups

	Description
RNF 44Mcg Three Times Weekly/ RNF 44Mcg Three Times Weekly(OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year open label extension (OLE). Participants who had received RNF three times a week in the core REFLEX trial, were re-titrated with a single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 36 months in this 12 months open label extension.
RNF 44 Mcg Once Weekly/RNF 44 Mcg Three Times Weekly (OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year OLE. Participants who had received RNF once weekly in the core REFLEX trial were re-titrated with a single dose of RNF injection 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 in this 12 months open label extension.
Placebo/RNF 44 Mcg Three Times Weekly (OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year OLE. Participants who had received placebo in the core REFLEX trial were re-titrated with a single dose of RNF injection 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 in this 12 months open label extension.

Measured Values

	RNF 44Mcg Three Times Weekly/RNF 44Mcg Three Times Weekly(OLE)	RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)	Placebo/RNF 44 Mcg Three Times Weekly (OLE)
Number of Participants Analyzed	4	5	11
Change From Baseline in Time Constant 2 (T2) Lesion Volume , Time Constant 1 (T1) Hypointense Lesion Volume and Gadolinium Enhanced (Gd+) Lesion Volume at Month 36			

	RNF 44Mcg Three Times Weekly/RNF 44Mcg Three Times Weekly(OLE)	RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)	Placebo/RNF 44 Mcg Three Times Weekly (OLE)
[units: cubic millimeter (mm^3)] Mean (Standard Deviation)			
T2 lesion volume at Baseline (n=4,5,11)	675.20 (940.87)	1703.48 (1324.41)	3533.37 (3914.98)
T2 lesion volume change at Month 36 (n=2,4,8)	180.25 (198.34)	-22.63 (382.14)	-1155.63 (3348.36)
T1 lesion volume at Baseline (n=4,5,11)	30.05 (60.10)	302.70 (358.58)	488.72 (589.06)
T1 lesion volume change at Month 36 (n=2,4,8)	55.75 (78.84)	216.68 (310.06)	138.89 (339.99)
Gd+ lesion volume at Baseline (n=4,5,11)	103.70 (151.17)	0.00 (0.00)	287.15 (649.68)
Gd+ lesion volume change at Month 36 (n=2,4,8)	-47.20 (66.75)	0.00 (0.00)	-246.08 (848.99)

7. Secondary Outcome Measure:

Measure Title	Change From Baseline in Expanded Disability Status Score (EDSS) Score at Month 36
Measure 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 at Month 36 was calculated as EDSS at Month 36 minus EDSS at baseline.
Time Frame	Baseline, Month 36
Safety Issue?	No

Analysis Population Description

OL ITT population included all participants who were randomized at baseline in core REFLEX trial and entered the 12 months OLE period. "n" signifies those participants who were evaluated for this measure at the specified time point for each arm group respectively.

Reporting Groups

	Description
RNF 44Mcg Three Times Weekly/ RNF 44Mcg Three Times Weekly(OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year open label extension (OLE). Participants who had received RNF three times a week in the core REFLEX trial, were re-titrated with a single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 36 months in this 12 months open label extension.

	Description
RNF 44 Mcg Once Weekly/RNF 44 Mcg Three Times Weekly (OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year OLE. Participants who had received RNF once weekly in the core REFLEX trial were re-titrated with a single dose of RNF injection 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 in this 12 months open label extension.
Placebo/RNF 44 Mcg Three Times Weekly (OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year OLE. Participants who had received placebo in the core REFLEX trial were re-titrated with a single dose of RNF injection 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 in this 12 months open label extension.

Measured Values

	RNF 44Mcg Three Times Weekly/RNF 44Mcg Three Times Weekly(OLE)	RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)	Placebo/RNF 44 Mcg Three Times Weekly (OLE)
Number of Participants Analyzed	4	5	11
Change From Baseline in Expanded Disability Status Score (EDSS) Score at Month 36 [units: unit on a scale] Mean (Standard Deviation)			
Baseline (n=4,5,11)	1.88 (0.85)	1.60 (0.96)	1.64 (0.67)
Change at Month 36 (n=2,4,8)	-0.25 (1.06)	-0.63 (0.48)	-0.50 (0.65)

Reported Adverse Events

Time Frame	[Not specified]
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 an Investigational Medicinal Product (IMP), regardless of causal relationship and even if no IMP has been administered.

Reporting Groups

	Description
RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)	Single dose of fetal bovine serum [FBS]-free/human serum albumin [HSA]-free formulation of interferon [IFN]-beta-1a (RNF) injection 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 24 months or until conversion to CDMS whichever occurs first.
RNF 44 Mcg Once Weekly (DB Population)	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 finally 44 mcg until 24 months or until conversion to CDMS whichever occurs first.
Placebo (DB Population)	Single dose of matching placebo administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 24 months or until conversion to CDMS whichever occurs first.
RNF 44 Mcg Three Times Weekly/OL RNF 44 Mcg Three Times Weekly	After having converted to CDMS, participants 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 24 months.
RNF 44 Mcg Once Weekly/OL RNF 44 Mcg Three Times Weekly	After having converted to CDMS, participants 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 24 months.
Placebo/OL RNF 44 Mcg Three Times Weekly	After having converted to CDMS, participants 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 24 months.
RNF 44Mcg Three Times Weekly/ RNF 44Mcg Three Times Weekly(OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year open label extension (OLE). Participants who had received RNF three times a week in the core REFLEX trial, were re-titrated with a single dose of RNF injection administered subcutaneously three times weekly at least 48 hours apart at a starting dose of 8.8 mcg for first 2 weeks followed by 22 mcg for next 2 weeks and finally 44 mcg until 36 months in this 12 months open label extension.
RNF 44 Mcg Once Weekly/RNF 44 Mcg Three Times Weekly (OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year OLE. Participants who had received RNF once weekly in the core REFLEX trial were re-titrated with a single dose of RNF injection 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 in this 12 months open label extension.
Placebo/RNF 44 Mcg Three Times Weekly (OLE)	Participants who were not converted to CDMS and completed 24 month core REFLEX trial were enrolled in a 1 year OLE. Participants who had received placebo in the core REFLEX trial were re-titrated with a single dose of RNF injection 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 in this 12 months open label extension.

Serious Adverse Events

	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)		RNF 44 Mcg Once Weekly (DB Population)		Placebo (DB Population)		RNF 44 Mcg Three Times Weekly/OL RNF 44 Mcg Three Times Weekly		RNF 44 Mcg Once Weekly/OL RNF 44 Mcg Three Times Weekly		Placebo/OL RNF 44 Mcg Three Times Weekly	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	6/171 (3.51%)		8/173 (4.62%)		12/171 (7.02%)		1/31 (3.23%)		0/30 (0%)		1/59 (1.69%)	
Blood and lymphatic system disorders												
Iron deficiency anemia [A] †	0/171 (0%)	0	1/173 (0.58%)	1	0/171 (0%)	0	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Cardiac disorders												
Acute myocardial infarction [A] †	1/171 (0.58%)	1	0/173 (0%)	0	0/171 (0%)	0	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Angina unstable [A] †	0/171 (0%)	0	0/173 (0%)	0	1/171 (0.58%)	1	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Congenital, familial and genetic disorders												
Deafness congenital [A] †	1/171 (0.58%)	1	0/173 (0%)	0	0/171 (0%)	0	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Dermoid cyst [A] †	1/171 (0.58%)	1	0/173 (0%)	0	0/171 (0%)	0	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Ear and labyrinth disorders												
Hypoacusis [A] †	0/171 (0%)	0	1/173 (0.58%)	1	0/171 (0%)	0	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Gastrointestinal disorders												
Gastrointestinal motility disorder [A] †	0/171 (0%)	0	0/173 (0%)	0	1/171 (0.58%)	1	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Inguinal hernia [A] †	0/171 (0%)	0	0/173 (0%)	0	1/171 (0.58%)	1	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Pancreatic necrosis [A] †	0/171 (0%)	0	0/173 (0%)	0	1/171 (0.58%)	1	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Hepatobiliary disorders												

	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)		RNF 44 Mcg Once Weekly (DB Population)		Placebo (DB Population)		RNF 44 Mcg Three Times Weekly/OL RNF 44 Mcg Three Times Weekly		RNF 44 Mcg Once Weekly/OL RNF 44 Mcg Three Times Weekly		Placebo/OL RNF 44 Mcg Three Times Weekly	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Cholelithiasis [A] †	0/171 (0%)	0	0/173 (0%)	0	0/171 (0%)	0	1/31 (3.23%)	1	0/30 (0%)	0	0/59 (0%)	0
Infections and infestations												
Appendicitis [A] †	3/171 (1.75%)	3	0/173 (0%)	0	0/171 (0%)	0	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Tonsillitis [A] †	1/171 (0.58%)	1	0/173 (0%)	0	0/171 (0%)	0	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Varicella [A] †	0/171 (0%)	0	1/173 (0.58%)	1	0/171 (0%)	0	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Injury, poisoning and procedural complications												
Muscle rupture [A] †	0/171 (0%)	0	1/173 (0.58%)	1	0/171 (0%)	0	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Post procedural hematoma [A] †	0/171 (0%)	0	0/173 (0%)	0	1/171 (0.58%)	1	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Tibia fracture [A] †	0/171 (0%)	0	1/173 (0.58%)	1	0/171 (0%)	0	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)												
Breast cancer stage III [A] †	0/171 (0%)	0	0/173 (0%)	0	1/171 (0.58%)	1	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Ovarian germ cell teratoma benign [A] †	0/171 (0%)	0	0/173 (0%)	0	1/171 (0.58%)	1	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Testis cancer [A] †	0/171 (0%)	0	0/173 (0%)	0	1/171 (0.58%)	1	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Nervous system disorders												
Ischemic stroke [A] †	0/171 (0%)	0	0/173 (0%)	0	1/171 (0.58%)	1	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Pregnancy, puerperium and perinatal conditions												

	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)		RNF 44 Mcg Once Weekly (DB Population)		Placebo (DB Population)		RNF 44 Mcg Three Times Weekly/OL RNF 44 Mcg Three Times Weekly		RNF 44 Mcg Once Weekly/OL RNF 44 Mcg Three Times Weekly		Placebo/OL RNF 44 Mcg Three Times Weekly	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Abortion spontaneous [A] †	0/171 (0%)	0	1/173 (0.58%)	1	1/171 (0.58%)	1	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Psychiatric disorders												
Psychotic disorder [A] †	0/171 (0%)	0	0/173 (0%)	0	0/171 (0%)	0	0/31 (0%)	0	0/30 (0%)	0	1/59 (1.69%)	1
Reproductive system and breast disorders												
Cervical polyp [A] †	0/171 (0%)	0	1/173 (0.58%)	1	0/171 (0%)	0	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Ovarian cyst [A] †	0/171 (0%)	0	0/173 (0%)	0	2/171 (1.17%)	2	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Respiratory, thoracic and mediastinal disorders												
Nasal septum deviation [A] †	0/171 (0%)	0	1/173 (0.58%)	1	0/171 (0%)	0	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Tonsillar disorder [A] †	0/171 (0%)	0	1/173 (0.58%)	1	0/171 (0%)	0	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 13.0

	RNF 44Mcg Three Times Weekly/RNF 44Mcg Three Times Weekly(OLE)		RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)		Placebo/RNF 44 Mcg Three Times Weekly (OLE)	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Blood and lymphatic system disorders						
Iron deficiency anemia [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Cardiac disorders						

	RNF 44Mcg Three Times Weekly/RNF 44Mcg Three Times Weekly(OLE)		RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)		Placebo/RNF 44 Mcg Three Times Weekly (OLE)	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Acute myocardial infarction [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Angina unstable [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Congenital, familial and genetic disorders						
Deafness congenital [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Dermoid cyst [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Ear and labyrinth disorders						
Hypoacusis [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Gastrointestinal disorders						
Gastrointestinal motility disorder [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Inguinal hernia [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Pancreatic necrosis [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Hepatobiliary disorders						
Cholelithiasis [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Infections and infestations						
Appendicitis [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Tonsillitis [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Varicella [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Injury, poisoning and procedural complications						
Muscle rupture [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Post procedural hematoma [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Tibia fracture [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						

	RNF 44Mcg Three Times Weekly/RNF 44Mcg Three Times Weekly(OLE)		RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)		Placebo/RNF 44 Mcg Three Times Weekly (OLE)	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Breast cancer stage III [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Ovarian germ cell teratoma benign [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Testis cancer [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Nervous system disorders						
Ischemic stroke [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Pregnancy, puerperium and perinatal conditions						
Abortion spontaneous [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Psychiatric disorders						
Psychotic disorder [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Reproductive system and breast disorders						
Cervical polyp [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Ovarian cyst [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Respiratory, thoracic and mediastinal disorders						
Nasal septum deviation [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Tonsillar disorder [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 13.0

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)		RNF 44 Mcg Once Weekly (DB Population)		Placebo (DB Population)		RNF 44 Mcg Three Times Weekly/OL RNF 44 Mcg Three Times Weekly		RNF 44 Mcg Once Weekly/OL RNF 44 Mcg Three Times Weekly		Placebo/OL RNF 44 Mcg Three Times Weekly	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	149/171 (87.13%)		156/173 (90.17%)		133/171 (77.78%)		20/31 (64.52%)		20/30 (66.67%)		47/59 (79.66%)	
Blood and lymphatic system disorders												
Iron deficiency anaemia [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Leukopenia [A] †	0/171 (0%)	0	0/173 (0%)	0	0/171 (0%)	0	3/31 (9.68%)	3	3/30 (10%)	3	2/59 (3.39%)	4
Lymphopenia [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Neutropenia [A] †	13/171 (7.6%)	15	6/173 (3.47%)	7	1/171 (0.58%)	1	0/31 (0%)	0	2/30 (6.67%)	2	3/59 (5.08%)	5
Thrombocytopenia [A] †	0/171 (0%)	0	0/173 (0%)	0	0/171 (0%)	0	1/31 (3.23%)	1	3/30 (10%)	3	1/59 (1.69%)	1
Endocrine disorders												
Hyperthyroidism [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Gastrointestinal disorders												
Aphthous stomatitis [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Constipation [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Diarrhea [A] †	4/171 (2.34%)	5	4/173 (2.31%)	5	9/171 (5.26%)	9	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Nausea [A] †	0/171 (0%)	0	0/173 (0%)	0	0/171 (0%)	0	0/31 (0%)	0	2/30 (6.67%)	4	1/59 (1.69%)	1
Toothache [A] †	6/171 (3.51%)	7	10/173 (5.78%)	12	6/171 (3.51%)	9	2/31 (6.45%)	2	1/30 (3.33%)	1	0/59 (0%)	0

	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)		RNF 44 Mcg Once Weekly (DB Population)		Placebo (DB Population)		RNF 44 Mcg Three Times Weekly/OL RNF 44 Mcg Three Times Weekly		RNF 44 Mcg Once Weekly/OL RNF 44 Mcg Three Times Weekly		Placebo/OL RNF 44 Mcg Three Times Weekly	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
General disorders												
Asthenia [A] †	9/171 (5.26%)	11	6/173 (3.47%)	9	5/171 (2.92%)	5	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Chills [A] †	11/171 (6.43%)	26	9/173 (5.2%)	27	5/171 (2.92%)	11	0/31 (0%)	0	2/30 (6.67%)	4	0/59 (0%)	0
Fatigue [A] †	13/171 (7.6%)	25	5/173 (2.89%)	12	11/171 (6.43%)	26	4/31 (12.9%)	5	1/30 (3.33%)	2	2/59 (3.39%)	2
Influenza like illness [A] †	93/171 (54.39%)	218	122/173 (70.52%)	374	34/171 (19.88%)	50	8/31 (25.81%)	9	3/30 (10%)	6	24/59 (40.68%)	31
Injection site erythema [A] †	50/171 (29.24%)	76	34/173 (19.65%)	49	3/171 (1.75%)	3	4/31 (12.9%)	5	3/30 (10%)	5	13/59 (22.03%)	13
Injection site pain [A] †	0/171 (0%)	0	0/173 (0%)	0	0/171 (0%)	0	2/31 (6.45%)	2	0/30 (0%)	0	0/59 (0%)	0
Pyrexia [A] †	6/171 (3.51%)	13	22/173 (12.72%)	29	9/171 (5.26%)	12	0/31 (0%)	0	2/30 (6.67%)	2	2/59 (3.39%)	4
Infections and infestations												
Influenza [A] †	9/171 (5.26%)	12	10/173 (5.78%)	17	17/171 (9.94%)	20	2/31 (6.45%)	2	0/30 (0%)	0	2/59 (3.39%)	2
Nasopharyngitis [A] †	17/171 (9.94%)	21	23/173 (13.29%)	30	22/171 (12.87%)	49	2/31 (6.45%)	2	1/30 (3.33%)	1	4/59 (6.78%)	4
Pharyngitis [A] †	9/171 (5.26%)	10	5/173 (2.89%)	9	10/171 (5.85%)	11	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Rhinitis [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Upper respiratory tract infection [A] †	17/171 (9.94%)	37	13/173 (7.51%)	19	20/171 (11.7%)	34	3/31 (9.68%)	6	1/30 (3.33%)	1	3/59 (5.08%)	3
Urinary tract infection [A] †	0/171 (0%)	0	0/173 (0%)	0	0/171 (0%)	0	2/31 (6.45%)	2	0/30 (0%)	0	0/59 (0%)	0

	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)		RNF 44 Mcg Once Weekly (DB Population)		Placebo (DB Population)		RNF 44 Mcg Three Times Weekly/OL RNF 44 Mcg Three Times Weekly		RNF 44 Mcg Once Weekly/OL RNF 44 Mcg Three Times Weekly		Placebo/OL RNF 44 Mcg Three Times Weekly	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Viral upper respiratory tract infection [A] †	9/171 (5.26%)	19	6/173 (3.47%)	12	8/171 (4.68%)	18	1/31 (3.23%)	1	2/30 (6.67%)	7	1/59 (1.69%)	4
Injury, poisoning and procedural complications												
Contusion [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Facial bones fracture [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Fall [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Limb injury [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Investigations												
Alanine aminotransferase increased [A] †	14/171 (8.19%)	15	11/173 (6.36%)	12	5/171 (2.92%)	6	3/31 (9.68%)	3	3/30 (10%)	3	3/59 (5.08%)	3
Anti-thyroid antibody positive [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Aspartate aminotransferase increased [A] †	10/171 (5.85%)	11	9/173 (5.2%)	10	3/171 (1.75%)	3	3/31 (9.68%)	3	1/30 (3.33%)	1	4/59 (6.78%)	4
Blood creatine phosphokinase increased [A] †	0/171 (0%)	0	0/173 (0%)	0	0/171 (0%)	0	0/31 (0%)	0	0/30 (0%)	0	3/59 (5.08%)	3
Musculoskeletal and connective tissue disorders												
Arthralgia [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Myalgia [A] †	12/171 (7.02%)	21	11/173 (6.36%)	17	8/171 (4.68%)	8	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0

	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)		RNF 44 Mcg Once Weekly (DB Population)		Placebo (DB Population)		RNF 44 Mcg Three Times Weekly/OL RNF 44 Mcg Three Times Weekly		RNF 44 Mcg Once Weekly/OL RNF 44 Mcg Three Times Weekly		Placebo/OL RNF 44 Mcg Three Times Weekly	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Pain in extremity [A] †	0/171 (0%)	0	0/173 (0%)	0	0/171 (0%)	0	0/31 (0%)	0	0/30 (0%)	0	3/59 (5.08%)	6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)												
Melanocytic naevus [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Nervous system disorders												
Cervicobrachial syndrome [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Headache [A] †	46/171 (26.9%)	145	37/173 (21.39%)	129	46/171 (26.9%)	135	3/31 (9.68%)	20	2/30 (6.67%)	2	5/59 (8.47%)	14
Migraine [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Paresthesia [A] †	7/171 (4.09%)	16	8/173 (4.62%)	17	16/171 (9.36%)	27	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Syncope [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Psychiatric disorders												
Anxiety [A] †	10/171 (5.85%)	10	7/173 (4.05%)	21	14/171 (8.19%)	20	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Depression [A] †	14/171 (8.19%)	17	9/173 (5.2%)	10	10/171 (5.85%)	10	0/31 (0%)	0	0/30 (0%)	0	0/59 (0%)	0
Nervousness [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Reproductive system and breast disorders												
Vulvovaginal pruritus [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Respiratory, thoracic and mediastinal disorders												

	RNF 44 Mcg Three Times Weekly (Double Blind [DB] Population)		RNF 44 Mcg Once Weekly (DB Population)		Placebo (DB Population)		RNF 44 Mcg Three Times Weekly/OL RNF 44 Mcg Three Times Weekly		RNF 44 Mcg Once Weekly/OL RNF 44 Mcg Three Times Weekly		Placebo/OL RNF 44 Mcg Three Times Weekly	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Oropharyngeal pain [A] †	6/171 (3.51%)	6	9/173 (5.2%)	13	11/171 (6.43%)	14	2/31 (6.45%)	2	0/30 (0%)	0	0/59 (0%)	0
Skin and subcutaneous tissue disorders												
Skin irritation [A] †	0/171 (0%)		0/173 (0%)		0/171 (0%)		0/31 (0%)		0/30 (0%)		0/59 (0%)	
Vascular disorders												
Hypertension [A] †	0/171 (0%)	0	0/173 (0%)	0	0/171 (0%)	0	0/31 (0%)	0	3/30 (10%)	3	1/59 (1.69%)	1

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 13.0

	RNF 44Mcg Three Times Weekly/RNF 44Mcg Three Times Weekly(OLE)		RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)		Placebo/RNF 44 Mcg Three Times Weekly (OLE)	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	3/4 (75%)		2/5 (40%)		5/11 (45.45%)	
Blood and lymphatic system disorders						
Iron deficiency anaemia [A] †	0/4 (0%)		0/5 (0%)		1/11 (9.09%)	
Leukopenia [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Lymphopenia [A] †	1/4 (25%)		0/5 (0%)		1/11 (9.09%)	
Neutropenia [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Thrombocytopenia [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Endocrine disorders						
Hyperthyroidism [A] †	1/4 (25%)		0/5 (0%)		1/11 (9.09%)	
Gastrointestinal disorders						

	RNF 44Mcg Three Times Weekly/RNF 44Mcg Three Times Weekly(OLE)		RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)		Placebo/RNF 44 Mcg Three Times Weekly (OLE)	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Aphthous stomatitis [A] †	1/4 (25%)		0/5 (0%)		0/11 (0%)	
Constipation [A] †	0/4 (0%)		0/5 (0%)		1/11 (9.09%)	
Diarrhea [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Nausea [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Toothache [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
General disorders						
Asthenia [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Chills [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Fatigue [A] †	0/4 (0%)		0/5 (0%)		1/11 (9.09%)	
Influenza like illness [A] †	1/4 (25%)		1/5 (20%)		1/11 (9.09%)	
Injection site erythema [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Injection site pain [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Pyrexia [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Infections and infestations						
Influenza [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Nasopharyngitis [A] †	0/4 (0%)		0/5 (0%)		1/11 (9.09%)	
Pharyngitis [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Rhinitis [A] †	0/4 (0%)		0/5 (0%)		1/11 (9.09%)	
Upper respiratory tract infection [A] †	0/4 (0%)		0/5 (0%)		1/11 (9.09%)	
Urinary tract infection [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Viral upper respiratory tract infection [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	

	RNF 44Mcg Three Times Weekly/RNF 44Mcg Three Times Weekly(OLE)		RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)		Placebo/RNF 44 Mcg Three Times Weekly (OLE)	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Injury, poisoning and procedural complications						
Contusion [A] †	1/4 (25%)		0/5 (0%)		0/11 (0%)	
Facial bones fracture [A] †	1/4 (25%)		0/5 (0%)		0/11 (0%)	
Fall [A] †	0/4 (0%)		0/5 (0%)		1/11 (9.09%)	
Limb injury [A] †	0/4 (0%)		0/5 (0%)		1/11 (9.09%)	
Investigations						
Alanine aminotransferase increased [A] †	0/4 (0%)		0/5 (0%)		1/11 (9.09%)	
Anti-thyroid antibody positive [A] †	0/4 (0%)		1/5 (20%)		0/11 (0%)	
Aspartate aminotransferase increased [A] †	0/4 (0%)		0/5 (0%)		1/11 (9.09%)	
Blood creatine phosphokinase increased [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Musculoskeletal and connective tissue disorders						
Arthralgia [A] †	0/4 (0%)		0/5 (0%)		1/11 (9.09%)	
Myalgia [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Pain in extremity [A] †	0/4 (0%)		0/5 (0%)		1/11 (9.09%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Melanocytic naevus [A] †	1/4 (25%)		0/5 (0%)		0/11 (0%)	
Nervous system disorders						
Cervicobrachial syndrome [A] †	0/4 (0%)		0/5 (0%)		1/11 (9.09%)	
Headache [A] †	1/4 (25%)		0/5 (0%)		2/11 (18.18%)	
Migraine [A] †	0/4 (0%)		0/5 (0%)		1/11 (9.09%)	
Paresthesia [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	

	RNF 44Mcg Three Times Weekly/RNF 44Mcg Three Times Weekly(OLE)		RNF 44 Mcg Once Weekly/ RNF 44 Mcg Three Times Weekly (OLE)		Placebo/RNF 44 Mcg Three Times Weekly (OLE)	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Syncope [A] †	1/4 (25%)		0/5 (0%)		0/11 (0%)	
Psychiatric disorders						
Anxiety [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Depression [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Nervousness [A] †	0/4 (0%)		0/5 (0%)		1/11 (9.09%)	
Reproductive system and breast disorders						
Vulvovaginal pruritus [A] †	1/4 (25%)		0/5 (0%)		0/11 (0%)	
Respiratory, thoracic and mediastinal disorders						
Oropharyngeal pain [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	
Skin and subcutaneous tissue disorders						
Skin irritation [A] †	0/4 (0%)		0/5 (0%)		1/11 (9.09%)	
Vascular disorders						
Hypertension [A] †	0/4 (0%)		0/5 (0%)		0/11 (0%)	

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 13.0

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Sponsor has the right to publish any results communication in connection with the study. The PI shall submit any communications including study results to the sponsor for review 30 working days prior to communication submission. The sponsor can request the PI to modify or delete any sponsor's proprietary information. If the PI refuses the modification, the submission shall be postponed for 60 days from PI refusal, to provide the sponsor the opportunity to file a patent or seek legal remedies.

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