15 December 2011
EMA/46058/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rebif

interferon beta-1a
Procedure No. EMEA/H/C/136/II/88/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II Group of variations

Pursuant to Article 7.2.(b) of Commission Regulation (EC) No 1234/2008, Merck Serono Europe Ltd submitted to the European Medicines Agency on 15 June 2011 an application for a group of variations.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary or common name:**	**Presentations:**
Rebif	interferon beta-1a	See Annex A

The following variations were requested in the group:

Variations requested		**Type**
C.I.6 a)	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
B.II.e.5 a) 2	Change in pack size of the finished product – Change in the number of units (e.g. tablets, ampoules, etc.) in a pack – Change outside the range of the currently approved pack sizes	IB

The MAH proposed the update of sections 4.1, 4.2, 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) and sections 1 and 3 of the Package Leaflet to include information on a new indication, i.e. treatment of patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing relapsing multiple sclerosis. These updates affect the PI of the 44 mcg presentations (pre-filled syringe, pre-filled pen and cartridges) and the PI of the initiation pack presentations (pre-filled syringe, pre-filled pen and cartridges). In addition, minor editorial changes were implemented across the SmPC and the Package leaflet, and the DDPS version number was removed from Annex II.

At the same time, the MAH proposed the update of sections 4.2 and 6.5 of the SmPC for the pre-filled syringe (PFS) and pre-filled pen (PFP) initiation packs in order to add additional pack sizes of 2x22 mcg PFS + 2x8.8 mcg PFS and 2x22 mcg PFP + 2x8.8 mcg PFP. Labelling and Package Leaflet were proposed to be updated accordingly.

The requested group of variations proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Rapporteur: Tomas Salmonson Co-Rapporteur: George Aislaitner

1.2. Steps taken for the assessment

Submission date:	15 June 2011
Start of procedure:	26 June 2011
Rapporteur's preliminary assessment report circulated on:	19 August 2011
Co-Rapporteur's preliminary assessment report circulated on:	9 September 2011
Rapporteurs' Joint assessment report circulated on:	16 September 2011
Request for supplementary information and extension of timetable adopted by the CHMP on:	22 September 2011
MAH's responses submitted to the CHMP on:	13 October 2011
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	1 November 2011
CHMP opinion:	17 November 2011

2. List of Abbreviations and Definition of Terms

ACTH	Adrenocorticotropic hormone
AE	Adverse Event
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
BAbs	Binding Antibodies
CDMS	Clinically Definite Multiple Sclerosis
CI	Confidence Interval
CIS	Clinically Isolated Syndrome
CTCAE	Common Toxicity Criteria Adverse Event
CUA	Combined Unique Active
DB	Double-Blind
DDPS	Detailed Description of the Pharmacovigilance System
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
GCP	Good Clinical Practice
Gd	Gadolinium
HR	Hazard Ratio
HSA	Human Serum Albumin
IFN	Interferon
IMP	Investigational Medicinal Product
ITT	Intent-To-Treat
IVRS	Interactive Voice Response System
LOV	Last Observed Value
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite

NAbs	Neutralizing Antibodies
OL	Open-Label
ow	Once weekly
PFP	Pre-filled pen
PFS	Pre-filled syringe
PI	Product Information
PP	Per-Protocol
PSUR	Periodic Safety Update Report
RNF	Rebif HSA-free formulation (previously Rebif New Formulation)
SAE	Serious Adverse Event
sc	Subcutaneously, subcutaneous
SD	Standard Deviation
SE	Standard Error
SmPC	Summary of Product Characteristics
TEAE	Treatment-Emergent Adverse Event
tiw	Three times weekly
WBC	White Blood Cell

3. Background information on the procedure

3.1. Submission of the dossier

With this application the MAH proposed to add the following indication "Rebif is indicated for the treatment of a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing relapsing multiple sclerosis", with consequential changes to sections 4.2, 4.8 and 5.1 of the SmPC. This type II variation was initially grouped with a type IB variation to introduce two additional pack sizes (2x8.8 micrograms and 2x22 micrograms initiation packages) for the pre-filled syringe and pre-filled pen, corresponding to the first month supply of the 44 micrograms once weekly posology.

The type IB variation was withdrawn by the applicant at the time of response to the Request for Supplementary Information.

Information on Paediatric requirements

N.A.

Market Exclusivity

N.A.

Orphan Medicinal Products

N.A.

Scientific Advice

N.A.

4. Scientific discussion

4.1. Introduction

Rebif (interferon beta-1a) was approved in Europe on 4 May 1998. The currently approved indication is for the treatment of relapsing forms of MS. The recommended posology of Rebif is 44 micrograms, to be administered subcutaneously three times a week, whereas a lower dose of 22 micrograms three times a week is recommended for patients who cannot tolerate the higher dose in view of the treating specialist.

Rebif is currently not approved for patients at the early stage of the disease, i.e. when they experience a first single clinical, demyelinating event and the multiple sclerosis diagnosis is not yet confirmed.

It is widely acknowledged that irreparable damage to the central nervous system occurs from the earliest stages of multiple sclerosis, even before clinical manifestation when patients seemingly are doing well. This underlines the importance of treatment initiation as early as possible in the disease course.

This submission constitutes an extension of the current Rebif marketing authorisation to include the indication: *"Rebif is indicated for the treatment of a single demyelinating event with an active*

inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing relapsing multiple sclerosis".

4.2. Clinical aspects

4.2.1. Introduction

The MAH submitted results of one pivotal phase III study 27025 (REFLEX) in subjects with a single demyelinating event at high risk of converting to multiple sclerosis to support the indication *"treatment of a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing relapsing multiple sclerosis".*

GCP

The Clinical trial was performed in accordance with GCP as claimed by the MAH.

The MAH provided a statement to the effect that the clinical trial conducted outside the EU was carried out in accordance with the ethical standards of Directive 2001/20/EC.

4.2.2. Clinical efficacy

4.2.2.1. Main study

One pivotal clinical trial (study 27025, REFLEX) supported the efficacy and safety of Rebif in the indication applied for.

An overview of the study is provided in the table below.

Table 1

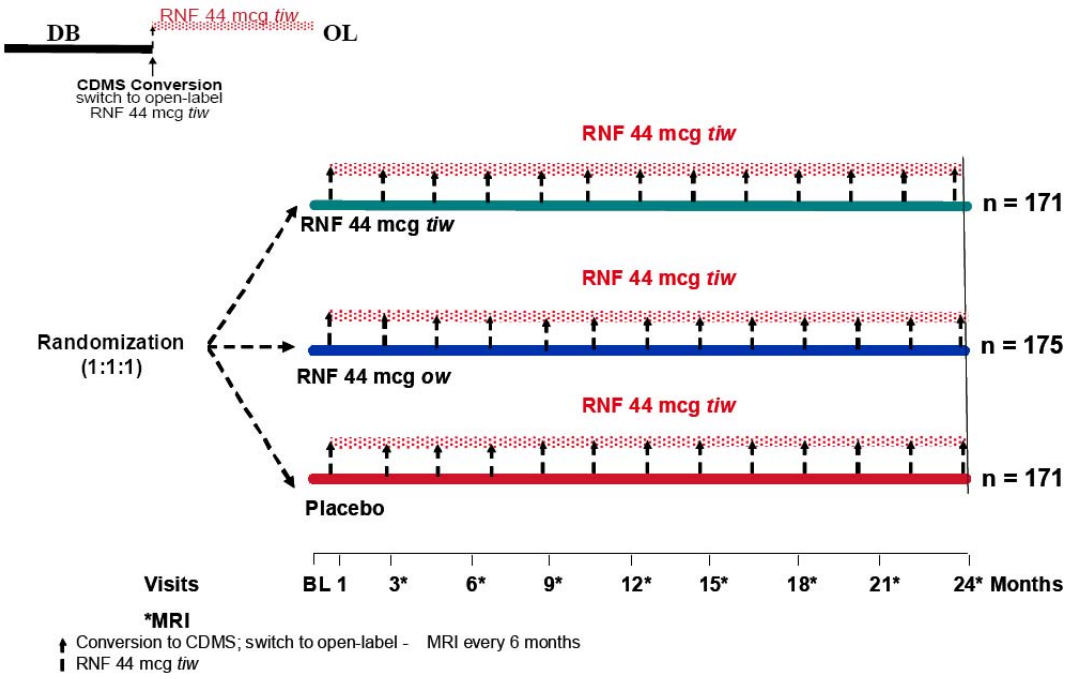
Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design & Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	IMP27025	5.3.5.1	Efficacy and Safety	Double-blind, randomized, placebo-controlled	Solution for injection in pre-filled syringes; Serum-free formulation (RNF); 44 mcg tiw , 44 mcg once weekly Placebo Subcutaneous	517	Patients with a first demyelinating event suggestive of MS	24 Months	Complete; Full

Methods

This was a Phase III, randomized, double-blind, placebo-controlled, multicenter clinical trial of RNF (44 mcg tiw and 44 mcg ow) in subjects considered at high risk of converting to multiple sclerosis. The double-blinded treatment duration was 24 months.

A schematic of the study design is shown in Figure 1 below.

Fig. 1 Trial Design of Study 27025 (REFLEX)



Study visits were scheduled at 1, 3, 6, 9, 12, 15, 18, 21 and 24 months post-baseline. Relapses were monitored on an ongoing basis. MRI scans were assessed at Screening and at Months 3, 6, 9, 12, 15, 18 and 24. If the patient reached CDMS prior to 24 months, MRI scans were performed at 6-month intervals following conversion.

A central neuroradiology centre performed the central blinded analysis of all MRI scans. A separate MRI-DSMB was to review all MRI scans that met the predefined alert criteria in order to provide appropriate recommendations for the protection of individual subjects.

Subjects reaching CDMS were switched to active treatment, at the approved 44 mcg sc tiw regimen.

The study utilized an independent Adjudication Committee, responsible for the following:

- eligibility assessment of individual subjects prior to randomization, based on the subjects' screening MRI and clinical status,
- confirmation of classification or reclassification of subjects' first demyelinating event into monofocal or multifocal (this was performed after randomization),
- adjudication of conversion to McDonald MS,
- adjudication of conversion to CDMS,
- confirmation of classification or reclassification of relapses as qualifying or non-qualifying.

Study Participants

The study enrolled adult male and female subjects 18 to 50 years of age, within 60 days following onset of a single, first clinical event suggestive of MS. The clinical event had to be a new neurological abnormality present for at least 24 hours, either mono- or polysymptomatic, other than paresthesia, vegetative or cerebral dysfunction. The T2-weighted MRI scan had to show at least 2 clinically silent

lesions, with a size of at least 3 mm, at least one of which was ovoid or periventricular or infratentorial. Subjects had to have an EDSS score between 0 and 5.0 (inclusive) before the start of treatment.

Subjects fulfilling the following criteria were excluded: a diagnosis of MS (as per McDonald criteria [2005]) or any other disease that could better explain the patient's signs and symptoms. Subjects with complete transverse myelitis or bilateral optic neuritis and subjects who had received prior immunomodulatory or immunosuppressant therapy were also excluded (subjects could have received oral or parenteral corticosteroids).

The CHMP considered that the revised McDonald criteria (2005) are widely accepted for a presumed diagnosis of MS under the prerequisite that they are applied to those patients with a typical clinically isolated syndrome (CIS) suggestive of MS or symptoms consistent with CNS inflammatory demyelinating disease and alternative diagnoses are excluded.

High risk was defined in the study protocol as having experienced an event suggestive of MS within 60 days prior to randomisation and presenting at least 2 clinically silent lesions on T2-weighted brain MRI. The CHMP considered that there is no standard definition of "high risk of converting" and that various criteria were applied in prior studies with other MS product; the issue of defining high risk patients is further discussed in the Discussion of clinical efficacy section).

Treatments

Subjects were allocated to one of 2 active dosage regimens (44 mcg tiw or ow) or matching placebo in a 1:1:1 randomization ratio. The blinded treatment duration was 24 months. Patients were titrated in accordance with the currently approved indication (8.8 mcg during the initial 2 weeks, 22 mcg during weeks 3 and 4, with the full dose administered from week 5 onward). Treatments were administered as subcutaneous injections using an auto-injector device, if possible at the same time (late afternoon or evening) on the same 3 days (e.g. Monday, Wednesday and Friday), as recorded by subjects using diary cards. Patients randomized to RNF 44 mcg ow were provided with one active dose and 2 placebo doses to mimic the tiw treatment.

If subjects converted to CDMS during the blinded treatment period, they were re-titrated to open-label treatment with RNF 44 mcg tiw for the remainder of the 24 months.

Concomitant Therapy

Subjects were recommended to take 400 mg of ibuprofen or 1000 mg of paracetamol/acetaminophen prophylactically with each injection during the first 12 weeks of treatment. If necessary, subjects could take additional doses every 4 to 6 hours thereafter during the first 24 hours (up to a maximum of 1200 mg ibuprofen or 3 g paracetamol/acetaminophen within any 24-hour period).

Subjects were treated with corticosteroids for relapses at the discretion of the treating physician. Any MRI scans conducted during the trial were to be performed before administration of steroids or at least 7 days after the last steroid dose.

Additional immunomodulatory or immunosuppressive therapy, chronic or monthly pulse corticosteroids, cytokines or anti-cytokine therapy, plasmaferesis, telbivudine or any experimental or off-label MS treatments were not allowed.

Objectives

The primary objective of the study was to evaluate the effect of RNF 44 mcg (tiw and ow) versus placebo on the time to conversion to McDonald multiple sclerosis in subjects with a first clinal demyelinating event at high risk of converting to MS.

The main secondary objective was to evaluate the effect of RNF 44 mcg (tiw and ow) versus placebo on the time to conversion to clinically definite multiple sclerosis (CDMS) in subjects with a first clinical demyelinating event at high risk of converting to MS.

Outcomes/endpoints

The primary efficacy endpoint of the study was the time to conversion to MS according to the revised McDonald criteria (2005), as confirmed by the independent Adjudication Committee. A subject was considered to have converted to MS according to the 2005 McDonald criteria if, following the first clinical demyelinating event, there was evidence of dissemination in space and in time based on a clinical event or on clinical data and MRI.

The main secondary endpoint was the time to conversion to clinically definite MS (CDMS). This was defined by either a second attack or a 3-month sustained increase (≥ 1.5 points) in the EDSS score (as confirmed by the independent Adjudication Committee).

The main MRI-based secondary endpoint was the mean number of Combined Unique Active (CUA) MRI lesions per subject per scan from randomization up to Month 24 or up to CDMS conversion, whichever occurred first.

Such MRI lesion was defined as a newly active or persistently active lesion found during a given scan on the PD/T2 sequence or the T1 Gd-enhancing sequence, without being double counted. As per the data collected, CUA MRI was computed by the sum of the new lesions and the persisting lesions on the T1 Gd-enhancing scan, plus the sum of the new lesions and the growing lesions on the PD/T2 scan not enhancing on the T1 Gd-enhancing scan. The mean number of CUA MRI lesions per subject per scan was calculated as the subject's total number of CUA lesions across all available scans during the DB period, divided by the subject's total number of available scans during that period.

Other secondary efficacy endpoints included the following:

- Mean number of new T2 lesions per subject per scan
- Mean number of new T1 lesions per subject per scan
- Mean number of new Gd-enhancing lesions per subject per scan
- T2 lesion volume
- T1 hypointense lesion volume
- T1 Gd-enhancing lesion volume
- Annualized relapse rate
- Proportion of relapse-free subjects during 12 months
- Proportion of relapse-free subjects during 24 months
- EDSS change from baseline over time
- Changes from baseline

The CHMP considered the primary and secondary endpoints acceptable and acknowledged the use of an independent Adjudication Committee in confirming the diagnosis.

Sample size

RNF 44 mcg tiw vs. placebo was considered the main treatment group comparison. It was estimated that a total of 450 subjects equally allocated to each of the 3 treatment groups (placebo, RNF 44 mcg ow and RNF 44 mcg tiw) would be required to achieve 165 events for the comparison of RNF 44 mcg tiw vs. placebo and 238 events in total (96 in placebo group, 73 in RNF 44 mcg ow group and 69 in RNF 44 mcg tiw group) after approximately 21 months of recruitment (assuming a recruitment of 30 subjects per month). This was to provide 90% power using a 2-sided log-rank test at a 0.05 alpha-error for detecting an HR of 0.6 in the primary efficacy endpoint for the main comparison RNF 44 mcg tiw vs. placebo, corresponding to an expected proportion of 15% free of conversion over 24 months in the placebo group and 32% in the RNF 44 mcg tiw group.

Assuming a withdrawal rate of 10% over 24 months, the planned sample size was increased to 480 subjects equally allocated to each of the 3 treatment groups (i.e., 160 subjects per group).

The sample size was considered acceptable by the CHMP.

Randomisation

Subjects were randomized on Day 1 in a ratio 1:1:1 to either RNF 44 mcg tiw, RNF 44 mcg ow or placebo tiw through a centralized IVRS system, using a minimization procedure to prevent imbalances between treatment groups and using the following a priori-defined stratification factors:

- Age (<30 years, ≥ 30 years),
- Classification of first clinical demyelinating event (monofocal, multifocal) according to the investigator,
- Steroid use at first clinical demyelinating event (yes, no),
- Presence of at least 1 Gd-enhancing lesion (yes, no) according to the central MRI reading centre.

The CHMP considered the randomisation and randomisation stratification factors acceptable and reflective of previous interferon studies.

Blinding (masking)

The study was conducted in a double-blind fashion. If subjects converted to clinically definite multiple sclerosis (CDMS) during the blinded period, they were switched and re-titrated to the recommended posology of Rebif 44 micrograms three times per week in an open label manner, while maintaining blinding as to their initial randomisation.

The evaluating physician conducting the neurological examinations and the neuro-radiology centre team assessing the MRI scans were blinded. Before the physician evaluated the subjects, all visible injection site reactions were covered by clothing; these site reactions were not examined by the evaluating physician.

The measures taken to maintain the blinding during the study were considered sufficient by the CHMP.

Statistical methods

The main analysis population for the efficacy endpoints was the ITT population, consisting of all randomized subjects. Subjects were analyzed according to their randomly allocated treatment.

The primary efficacy variable (time to conversion to McDonald MS) was analyzed by 2-sided stratified (by randomization stratification factors) log-rank test at the 0.05 significance level. The hazard ratio with 2-sided 95% CIs was estimated using an adjusted Cox's proportional hazards model using treatment and the stratification factors as covariates. Subjects who did not convert to McDonald MS within the 24-month trial period from randomization up to the Month 24 visit were considered as right-censored data. The date of the last available MRI assessment reported from randomization up to the Month 24 visit was used as time of censoring.

The secondary endpoint of time to CDMS was analyzed similarly.

For pair-wise comparisons for the secondary endpoint of CUA lesions, the treatment effect with corresponding 95% CIs was estimated using a negative binomial model including treatment and stratification factors as covariates. The p-value for this comparison was estimated using a non-parametric ANOVA on ranks model including treatment and stratification factors as covariates.

The primary efficacy endpoint (time to conversion to McDonald MS), time to conversion to CDMS and the main MRI-based efficacy endpoint (mean number of CUA lesions) were part of the hypothesis testing and type I error control using a hierarchical approach in the following sequence:

(I) RNF 44 mcg tiw vs. placebo for:

1. Time to McDonald MS at the first level of the hierarchy
2. Time to CDMS at the second level of the hierarchy
3. Mean number of CUA lesions per subject per scan at the third level of the hierarchy

(II) RNF 44 mcg ow vs. placebo for the same 3 endpoints in the same hierarchical order:

4. Time to McDonald MS at the first level of the hierarchy
5. Time to CDMS at the second level of the hierarchy
6. Mean number of CUA lesions per subject per scan at the third level of the hierarchy

The 6 confirmatory tests were 2-sided and performed at the 0.05 significance level in the pre-specified fixed sequence described above with confirmatory testing being continued if the current hypothesis (H0) in the sequence was rejected.

Changes in the Conduct of the Study or Planned Analyses

According to the study protocol, the MAH planned to conduct the first analysis for the main treatment group comparison (RNF 44 mcg tiw vs. placebo) when a total number of 107 conversions to CDMS were reached in the placebo group and RNF 44 mcg tiw group combined during the 24-month study period, as monitored by an independent statistician, unless the timing of this analysis would fall within 3 months of the 24-month analysis. The last projection received in December 2009 estimated that these 107 events would not be reached at least 3 months prior to the 24-month analysis and accordingly, the first analysis was not performed. The CHMP considered this approach acceptable.

Results

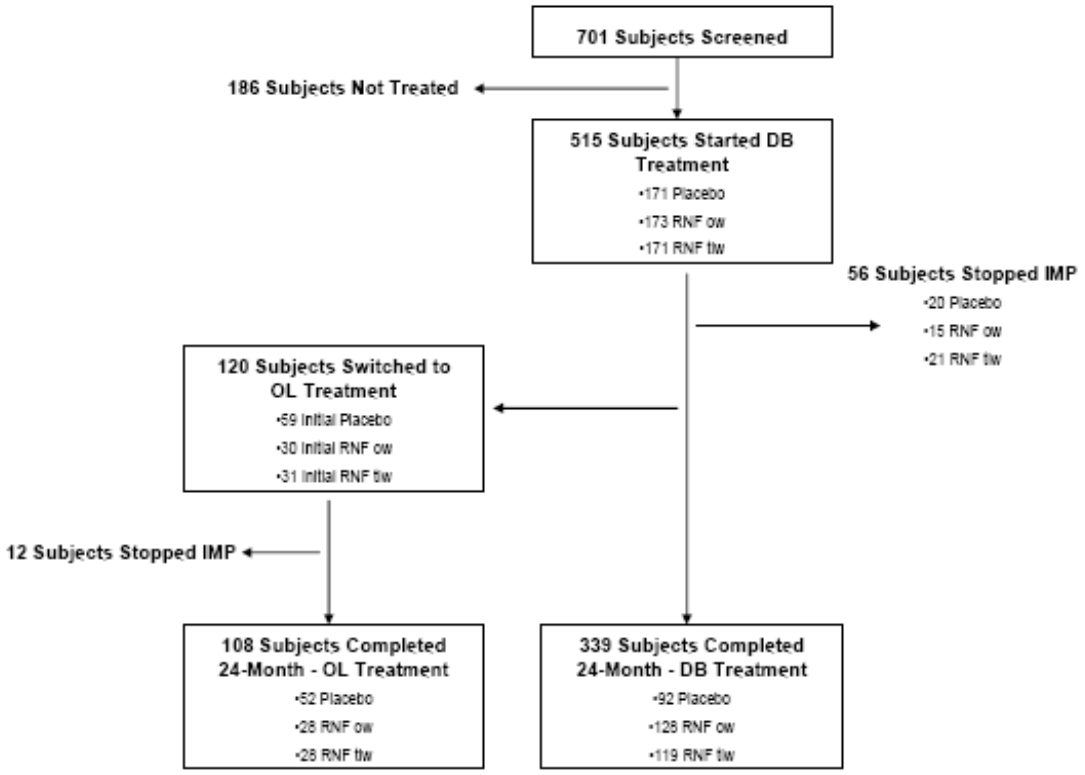
Recruitment

The study was performed between 16 November 2006 (first subject, first visit) and 13 August 2010 (last subject, last visit). Eighty study centres across 28 countries randomized one or more subjects.

Participant flow

A total of 517 subjects (ITT Population) were randomized and 515 subjects started the DB treatment (DB Safety Population), of which 339 subjects (65.8%) completed the 24-month DB treatment period; 120 subjects (23.3%) converted to CDMS and subsequently switched to OL RNF 44 mcg tiw (OL Safety Population) and 56 subjects (10.9%) prematurely discontinued treatment. The disposition of subjects is summarised in Figure 2.

Fig. 2 Disposition of subjects



Source: Table 15-19, Table 15-22 and Table 15-26

The subject populations and subject disposition (ITT population) are summarized in tables 2 and 3, respectively.

Table 2: 24-Month Analysis – Subject Populations

Population	Placebo	RNF 44 mcg ow	RNF 44 mcg tiw	Overall
Screened Population				701
Non-randomized Population				184 (26.2)
ITT Population [a]	171	175	171	517 (73.8)
PP Population [a] [d]	154 (90.1)	152 (86.9)	152 (88.9)	458 (88.6)
DB Safety Population [b]	171	173	171	515
- Randomized to Placebo [e]	170 (99.4)	0 (0.0)	0 (0.0)	
- Randomized to RNF 44 mcg ow [e]	0 (0.0)	173 (100.0)	1 (0.6)	
- Randomized to RNF 44 mcg tiw [e]	0 (0.0)	0 (0.0)	170 (99.4)	
- Non-randomized [e]	1 (0.6)	0 (0.0)	0 (0.0)	
OL Safety Population [b] [c] [e]	59 (34.5)	30 (17.3)	31 (18.1)	120 (23.3)

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(a) According to the treatment originally assigned by the IVRS.
(b) According to the treatment actually received during the DB period.
(c) All these subjects received RNF 44 mcg tiw during the OL period.
(d) Percentages are calculated as a proportion of the ITT population.
(e) Percentages are calculated as a proportion of the DB safety population.

Table 3: 24-Month Analysis – Subject Disposition (ITT Population)

Characteristic		Placebo (n=171) n (%)	RNF 44 mcg ow (n=175) n (%)	RNF 44 mcg tiw (n=171) n (%)	Overall (n=517) n (%)
Status at End of Whole Study Period	n (missing)	171 (0)	175 (0)	171 (0)	517 (0)
	Completed	146 (85.4)	156 (89.1)	146 (85.4)	448 (86.7)
	- Entered REFLEXION	133 (77.8)	142 (81.1)	127 (74.3)	402 (77.8)
	- Entered 1-year OL Follow-Up	4 (2.3)	5 (2.9)	11 (6.4)	20 (3.9)
	- Completed Safety Follow-Up	9 (5.3)	9 (5.1)	8 (4.7)	26 (5.0)
	Withdrew Prematurely	25 (14.6)	19 (10.9)	25 (14.6)	69 (13.3)

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Demographics and other Baseline Characteristics

Baseline characteristics for the ITT population are summarized in table 4. The treatment groups were similar with respect to demographic, clinical and MRI parameters.

Overall, EDSS scores of randomized subjects were balanced across treatment groups at baseline. The median EDSS score was 1.50 in the overall population, ranging from 0.0 to 4.0. The majority of subjects (83.9%) had a score between 1.0 and 2.5.

Table 4: Baseline Characteristics (ITT Population)

	Placebo (n=171)	RNF 44 mcg ow (n=175)	RNF 44 mcg tiw (n=171)
Female - % (n)	65.5% (112)	60.6% (106)	66.7% (114)
Age - median (quartiles)	29 (25-37)	30 (25-37)	29 (24-36)
Monofocal Onset* - % (n)	53.2% (91)	51.4% (90)	56.1% (96)
Steroid treatment - % (n)	70.8% (121)	70.3% (123)	70.8% (121)
>= 9 T_2 Lesions - % (n)	71.3% (122)	72.0% (126)	75.4% (129)
At least 1 Gd+ Lesion - % (n)	42.7% (73)	41.1% (72)	39.8% (68)

* As classified by the Independent Adjudication Committee (IAC)

Source: Refer to Table 11-1, Table 11-3, and Table 11-6 of the Study 27025 (REFLEX) CTR

A single screening MRI scan was performed at least 30 days after the clinical event suggestive of MS and 10 days prior to study day 1. In the overall study population, 58.8% of subjects had no T1 Gd-enhancing lesions, 17.6% of subjects had one lesion, 9.3% had two lesions and the remaining subjects had three or more lesions, with similar distribution across the treatment groups. The majority of subjects had at least 9 T2 lesions at screening. Furthermore, the majority of subjects received steroids for the first clinical event. The CHMP noted that there was consistency in the monofocal/ multifocal classification by the investigator and the Adjudication Committee. Overall, the CHMP was of the opinion that the study population was similar to that enrolled in other beta interferon studies and was representative of the population observed in clinical practice.

Outcomes and estimation

The main primary endpoint was the time to conversion to McDonald MS over 24 months, for RNF 44 mcg tiw and ow, as compared to placebo. The main secondary efficacy endpoint was the time to conversion to CDMS. The main efficacy results are summarized in table 5 and figures 3 and 4.

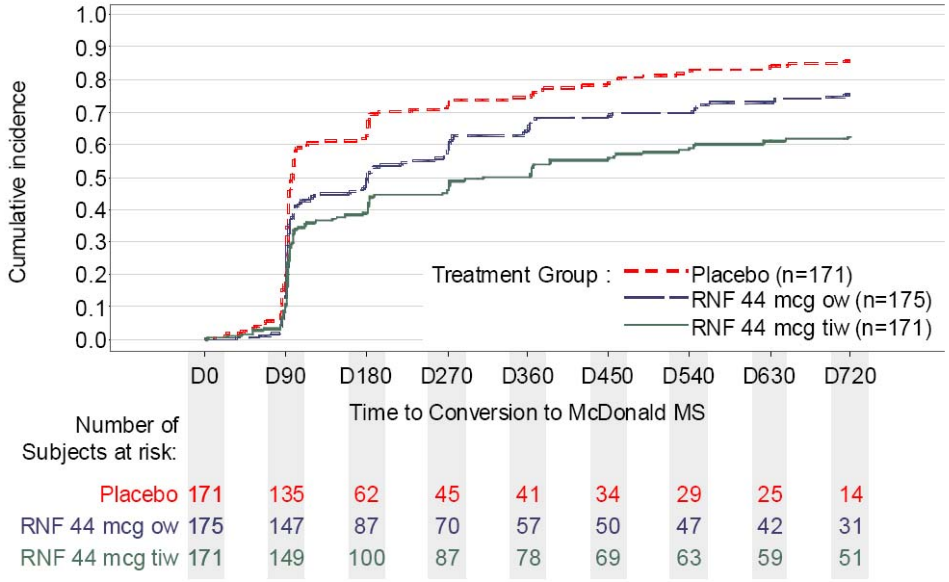
Table 5: Time to McDonald MS and CDMS (ITT Population)

	p-value*		Hazard Ratio [95% CI]		2-year cumulative probability, %		
	RNF 44mcg ow vs. Placebo	RNF 44mcg tiw vs. Placebo	RNF 44mcg ow	RNF 44mcg tiw	Placebo	RNF 44mcg ow	RNF 44mcg tiw
Time to McDonald MS	=0.008	<0.001	0.69 [0.54, 0.87]	0.49 [0.38, 0.64]	85.8	75.5	62.5
Time to CDMS	=0.002	<0.001	0.53 [0.35, 0.79]	0.48 [0.31, 0.73]	37.5	21.6	20.6

* Obtained by Log-rank test

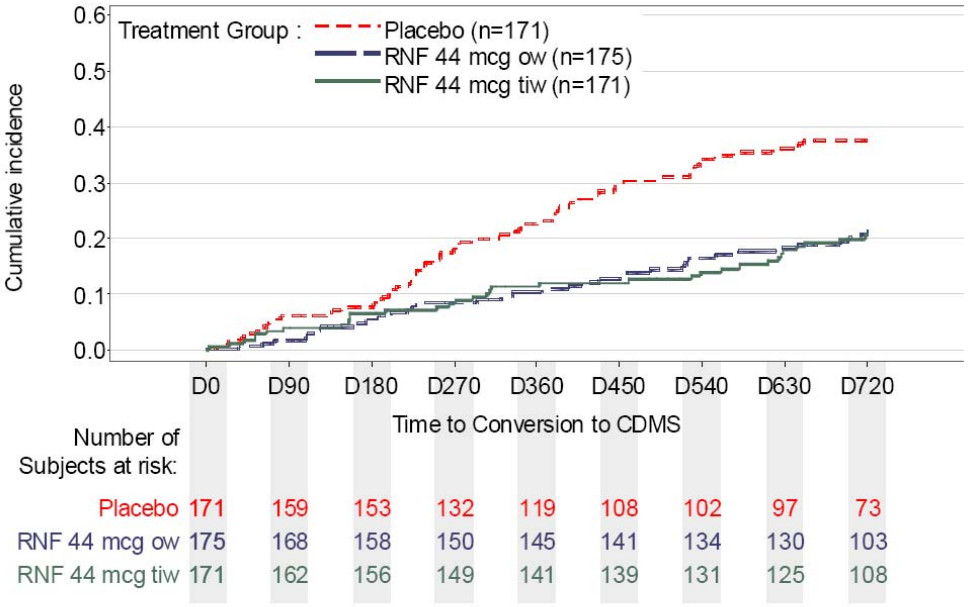
Source: Refer to Table 11-20 of Study 27025 (REFLEX) CTR

Fig. 3: Time to Conversion to McDonald MS – Kaplan-Meier Cumulative Incidence Curves (ITT Population)



Source: Refer to Figure 11-2 of the Study 27025 (REFLEX) CTR

Fig. 4 Time to Conversion to CDMS – Kaplan-Meier Cumulative Incidence Curves (ITT Population)



Source: Refer to Figure 11-3 of the Study 27025 (REFLEX) CTR

RNF 44 mcg tiw and RNF 44 mcg ow statistically significantly delayed the conversion from the first clinical event to McDonald MS as compared with placebo (adjusted log-rank test: p<0.001 and p=0.008, respectively). Based on Kaplan-Meier estimates, the cumulative probability of conversion to McDonald MS over 24 months was 85.8% in the placebo group compared to 62.5% and 75.5% in the RNF 44 mcg tiw and RNF 44 mcg ow groups, respectively.

Similarly, RNF 44 mcg tiw and RNF 44 mcg ow statistically significantly delayed the conversion from the first clinical event to CDMS as compared with placebo (adjusted log-rank test: p<0.001 and p=0.002, respectively). Based on Kaplan-Meier estimates, the cumulative probability of conversion to CDMS over 24 months was 37.5% in the placebo group compared to 20.6% and 21.6% in the RNF 44 mcg tiw and RNF 44 mcg ow groups, respectively.

In an exploratory analysis, comparing the RNF 44 mcg tiw group to the 44 mcg ow group indicated a difference between the dose groups for McDonald MS (HR = 0.71, 95% CI [0.54, 0.91], log-rank test: p=0.009). This difference was not observed for time to conversion to CDMS (RNF 44 mcg tiw vs. RNF 44 mcg ow: HR = 0.90, 95% CI [0.56, 1.43], log-rank p=0.774).

Sensitivity analyses

A number of sensitivity analyses were conducted for the primary endpoint including the following:

Unadjusted Analysis

Treatment group comparison and treatment effect estimate was further investigated using an unadjusted Cox's proportional hazards model. The pair-wise comparison of active treatment groups versus placebo using a 2-sided unstratified log-rank test showed a statistically significant delay in the time to conversion to McDonald MS in RNF 44 mcg tiw (p-value < 0.001) and ow (p-value = 0.004) treatment groups as compared to placebo.

Interval-Censored Analysis

Conversion to McDonald MS could take place at a fixed time point dictated by the timing of the MRIs (every 3 months) or at the occurrence of the second clinical attack which could occur within an interval of time defined by visits. Additional sensitivity analysis was performed using statistical methods dealing with interval-censored type of data as parametric estimations using Weibull modelling. Parameter estimates using both the adjusted and unadjusted Weibull models with interval censoring showed a statistically significant reduction of the risk of converting to McDonald MS over 24 months both for RNF 44 mcg tiw (p-value <0.001) and RNF 44 mcg ow (p-value = 0.001) compared to placebo.

Analysis based on Initial Cut-Off Date

As the original First Analysis based on the McDonald conversions prior to Protocol Amendment 5 was performed at the same time as the 24-Month Analysis (as per Amendment 5), the number of conversions to McDonald MS at the time of analysis was higher, providing higher power than initially defined. Therefore, the primary analysis of the primary efficacy endpoint and the secondary analysis of the primary efficacy endpoint were also performed based on the initial cut-off date defined by the date when the 165 conversions to McDonald MS originally required were accumulated in the placebo group and the RNF 44 mcg tiw group combined. The results of these analyses were comparable.

Per-Protocol Analysis

The primary and secondary analyses of the primary efficacy endpoint, the unadjusted analysis and the interval-censored analysis of the primary efficacy endpoint (as described above) were also performed on the PP Population, defined as all subjects from the ITT population who did not have any major protocol deviations likely to interfere with the efficacy assessment of the primary efficacy endpoint.

The CHMP considered the results of sensitivity analyses to be consistent with the primary analyses.

Subgroup analyses

The primary (time to McDonald MS) and main secondary (time to CDMS) efficacy endpoints were analyzed by subgroup, using the randomization stratification factors: age (<30 years, ≥30 years), classification of first clinical demyelinating event (Monofocal, Multifocal), steroid use at first demyelinating event (Yes, No) and presence of at least 1 Gd-enhancing lesion at screening (Yes, No). Additional subgroup analyses based on other (a priori defined) factors included number of T2 lesions at screening visit (<9 T2 lesions, ≥9 T2 lesions) and gender (Male, Female). The results are summarized in Tables 6 and 7 below.

Table 6: Time to Conversion to McDonald MS by Subgroup (ITT Population)

Subgroup	Number of Subjects			Risk (KM Estimates) at 2 years			RNF 44 mcg tiw vs. Placebo		RNF 44 mcg ow vs. Placebo	
	Placebo (n=171)	RNF 44 mcg tiw (n=171)	RNF 44 mcg ow (n=175)	Placebo	RNF 44 mcg tiw	RNF 44 mcg ow	HR (95% CI)	Absolute Risk Reduction	HR (95% CI)	Absolute Risk Reduction
ITT Population	**171**	**171**	**175**	**86%**	**62%**	**76%**	**0.49 [0.38 :0.64]*** **	**24%**	**0.69 [0.54 :0.87]** **	**10%**
Age Group										
<30	87	86	86	89%	66%	80%	0.52 [0.37 :0.74]***	23%	0.74 [0.53 :1.03]	9%
>=30	84	85	89	83%	59%	71%	0.52 [0.36 :0.74]***	24%	0.69 [0.49 :0.97]*	12%
Classification of First Clinical Demyelinating Event										
Monofocal	91	96	90	75%	54%	61%	0.58 [0.40 :0.84]**	21%	0.72 [0.50 :1.03]	14%
Multifocal	80	75	85	97%	73%	90%	0.45 [0.31 :0.64]***	24%	0.64 [0.47 :0.88]**	7%
Steroid Use at First Clinical Demyelinating Event										
Yes	121	120	125	86%	65%	74%	0.55 [0.41 :0.75]***	21%	0.71 [0.53 :0.94]*	12%
No	50	51	50	85%	56%	78%	0.44 [0.27 :0.72]***	29%	0.72 [0.46 :1.12]	7%
Presence of Gd Enhancing Lesions at Baseline										
Yes	73	68	72	94%	75%	85%	0.54 [0.38 :0.79]**	19%	0.66 [0.46 :0.93]*	9%
No	98	103	103	79%	54%	69%	0.49 [0.35 :0.70]***	25%	0.74 [0.53 :1.02]	10%
Number of T2 Lesions at Baseline										
< 9 T2 Lesions	49	42	49	62%	37%	40%	0.42 [0.22 :0.80]**	25%	0.51 [0.29 :0.91]*	22%
>= 9 T2 Lesions	122	129	126	96%	70%	89%	0.46 [0.35 :0.62]***	26%	0.71 [0.55 :0.93]*	7%
Gender										
Male	59	57	69	84%	72%	78%	0.71 [0.46 :1.08]	12%	0.92 [0.62 :1.37]	6%
Female	112	114	106	87%	58%	74%	0.44 [0.32 :0.61]***	29%	0.61 [0.45 :0.83]**	13%

*** p<0.001, ** p<0.01, * p<0.05
Source: refer to Table 15-90 through Table 15-96 of the Study 27025 CTR and data on file

Table 7: Time to Conversion to CDMS by Subgroup (ITT Population)

Subgroup	Number of Subjects			Risk (KM Estimates) at 2 years			RNF 44 mcg tiw vs. Placebo		RNF 44 mcg ow vs. Placebo	
	Placebo (n=171)	RNF 44 mcg tiw (n=171)	RNF 44 mcg ow (n=175)	Placebo	RNF 44 mcg tiw	RNF 44 mcg ow	HR (95% CI)	Absolute Risk Reduction	HR (95% CI)	Absolute Risk Reduction
ITT Population	**171**	**171**	**175**	**38%**	**21%**	**22%**	**0.48 [0.31;0.73]*** **	**17%**	**0.53 [0.35;0.79]** **	**16%**
Age										
<30	87	86	86	41%	20%	26%	0.43 [0.24;0.78]**	21%	0.56 [0.32;0.98]*	15%
>=30	84	85	89	34%	21%	18%	0.55 [0.30; 1.00]	13%	0.50 [0.27;0.92]*	16%
Classification of First Clinical Demyelinating Event										
Monofocal	91	96	90	32%	19%	17%	0.53 [0.29;0.98]*	13%	0.50 [0.27;0.93]*	15%
Multifocal	80	75	85	44%	23%	27%	0.45 [0.25;0.81]**	21%	0.54 [0.31;0.94]*	17%
Steroid Use at First Clinical Demyelinating Event										
Yes	121	120	125	39%	24%	22%	0.54 [0.33;0.87]*	15%	0.50 [0.31;0.81]**	17%
No	50	51	50	34%	12%	21%	0.33 [0.13;0.83]*	22%	0.60 [0.28;1.27]	13%
Presence of Gd Enhancing Lesion at Baseline										
Yes	73	68	72	46%	23%	20%	0.42 [0.23;0.78]**	23%	0.37 [0.20;0.68]**	26%
No	98	103	103	31%	19%	23%	0.55 [0.31;1.00]	12%	0.72 [0.41;1.26]	8%
Number of T2 Lesions at Baseline										
< 9 T2 Lesions	49	42	49	32%	16%	13%	0.43 [0.17;1.11]	16%	0.39 [0.15:1.01]	19%
>= 9 T2 Lesions	122	129	126	40%	22%	25%	0.49 [0.30;0.78]**	18%	0.56 [0.35;0.88]*	15%
Gender										
Male	59	57	69	38%	24%	26%	0.53 [0.27;1.07]	14%	0.61 [0.32;1.17]	12%
Female	112	114	106	37%	19%	19%	0.46 [0.27;0.78]**	18%	0.48 [0.28;0.82]**	18%

*** p<0.001, ** p<0.01, * p<0.05

Source: refer to Table 15-115, Table 15-116, Table 15-118, and Table 15-119 of the Study 27025 CTR, and data on file

The effect of RNF 44 mcg tiw on delaying the time to conversion to McDonald MS was maintained and statistically significant in all pre-defined subgroups except one (male [p=0.107]). The treatment effect of RNF 44 mcg ow did not reach statistical significance in several subgroups (<30 years [p=0.072]; monofocal [p=0.074]; no steroid use at first demyelinating event [p=0.142]; no Gd-enhancing lesion at baseline [p=0.069] and male [p=0.694]).

Statistically significant effects of RNF 44 mcg tiw on the time to CDMS were observed across the subgroups except for subjects with <9 T2 lesions at screening (p=0.081) and males (p=0.076). Regarding RNF 44 mcg ow for time to conversion to CDMS, statistical significance was not reached in some cases (no steroid use at first demyelinating event [p=0.180]; no Gd-enhancing lesion at baseline [p=0.251]; <9 T2 lesions at baseline [p=0.053] and male [p=0.138]).

Secondary MRI-based Endpoints

Mean number of CUA lesions

The main MRI-based secondary efficacy endpoint was the mean number of CUA lesions per subject per scan from randomization up to Month 24 or up to conversion to CDMS, whichever occurred first.

The main analysis of this endpoint consisted of the pair-wise comparison of the treatment groups at the 0.05 significance level using a non-parametric ANOVA on ranks model including treatment and randomization stratification factors as covariates.

Within the double-blind period, the treatment with RNF 44 mcg tiw and RNF 44 mcg ow reduced the mean number of CUA lesions per subject per scan ($p<0.001$ for both). The comparison between RNF 44 mcg tiw and RNF 44 mcg ow also showed statistically significant difference ($p=0.002$). The mean (SD) number of CUA lesions per subject per scan in the DB treatment period was 0.60 (1.15) in the RNF 44 mcg tiw treatment group, 1.23 (4.26) in the RNF 44 mcg ow treatment group, and 2.70 (5.23) in the placebo treatment group.

Table 8: CUA Lesions during the DB Period (ITT Population)

Characteristic	Statistics	Placebo (n=171)	RNF 44 mcg ow (n=175)	RNF 44 mcg tiw (n=171)
Cumulative Number of CUA Lesions				
	n (missing)	162 (9)	168 (7)	162 (9)
	Mean (SD)	12.4 (23.1)	5.6 (8.0)	3.6 (7.3)
	Median	5.0	3.0	1.0
	Q1; Q3	2.0; 12.0	1.0; 7.0	0.0; 4.0
	Min; Max	0; 226	0; 52	0; 74
Mean Number of CUA Lesions per Subject per Scan				
	n (missing)	162 (9)	168 (7)	162 (9)
	Mean (SD)	2.70 (5.23)	1.23 (4.26)	0.60 (1.15)
	Median	1.00	0.40	0.25
	Q1; Q3	0.25; 2.50	0.13; 1.13	0.00; 0.75
	Min; Max	0.0; 40.0	0.0; 52.0	0.0; 9.3
	Treatment Group Comparison, p-value [a]			
	- RNF 44 mcg tiw versus Placebo		<0.001	
	- RNF 44 mcg ow versus Placebo		<0.001	
	- RNF 44 mcg tiw versus RNF 44 mcg ow		0.002	

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(a) p-values were estimated using a 2 sided stratified non-parametric ANOVA model on ranked data with effects for treatment group and the randomization stratification factors [b].

(b) Randomization stratification factors:
- age (<30 years, >=30 years),
- classification of first clinical demyelinating event (monofocal, multifocal),
- steroid use at first clinical demyelinating event (yes, no),
- and presence of Gd enhancing lesions at baseline (yes, no).

Other secondary efficacy variables

The mean number of new T2 lesions per subject per scan was significantly lower in subjects randomized to RNF 44 mcg tiw (0.50) and in subjects randomized to RNF 44 mcg ow (0.59) than in subjects randomized to Placebo (1.35).

The mean number of new T1 hypointense lesions per subject per scan was significantly lower in subjects randomized to RNF 44 mcg tiw (0.35) and in subjects randomized to RNF 44 mcg ow (0.46) than in subjects randomized to placebo (0.84).

The mean number of new Gd-enhancing lesions per subject per scan was significantly lower in subjects randomized to RNF 44 mcg tiw (0.16) and in subjects randomized to RNF 44 mcg ow (0.35) than in subjects randomized to placebo (0.97).

Over the duration of 24 months in subjects with a first demyelinating event, small changes in EDSS scores were observed in all treatment groups over the entire study period, showing a mean change in EDSS score of -0.09 in the RNF 44 mcg tiw treatment group, 0.01 in the RNF 44 mcg ow treatment group and 0.14 in the placebo treatment group. No clinically significant changes were observed for MSFC or its individual components.

4.2.3. Discussion of clinical efficacy

The MAH submitted results of study 27025 (a double-blind, placebo-controlled trial comparing RNF 44 mcg tiw and 44 mcg ow vs. placebo in patients with CIS) to support the following indication:

Rebif is indicated for the treatment of patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing relapsing multiple sclerosis (see section 5.1).

With respect to clinical efficacy, the CHMP considered that RNF 44 mcg tiw and RNF 44 mcg ow statistically significantly delayed the conversion from the first clinical event to McDonald MS as compared with placebo (adjusted log-rank test: $p<0.001$ and $p=0.008$, respectively). Based on Kaplan-Meier estimates, the cumulative probability of conversion to McDonald MS over 24 months was 85.8% in the placebo group compared to 62.5% and 75.5% in the RNF 44 mcg tiw and RNF 44 mcg ow groups, respectively.

Similarly, RNF 44 mcg tiw and RNF 44 mcg ow statistically significantly delayed the conversion from the first clinical event to CDMS as compared with placebo ($p<0.001$ and $p=0.002$, respectively). The cumulative probability of conversion to CDMS over 24 months was 37.5% in the placebo group compared to 20.6% and 21.6% in the RNF 44 mcg tiw and RNF 44 mcg ow groups, respectively.

Thus, the CHMP was of the opinion that both dosing regimens of Rebif were indicative of an effect in delaying time to McDonald MS (2005) and time to CDMS in the study population enrolled.

Subjects had to have an EDSS score between 0 and 5.0 (inclusive) before the start of treatment. The mean baseline EDSS score was 1.53 in the placebo treatment group, 1.50 in the RNF 44 mcg ow treatment group and 1.51 in the RNF 44 mcg tiw treatment group. The median (Q1; Q3) baseline EDSS score was 1.50 (1.00; 2.00) in all treatment groups. Over the duration of 24 months in subjects with a first demyelinating event, only small changes in EDSS scores were observed in all treatment groups over the entire study period, although this endpoint reached statistical significance ($p=0.011$) for RNF 44 mcg tiw vs. placebo at last observed value during the DB period (mean change in EDSS score: -0.09 in the RNF 44 mcg tiw treatment group, 0.01 in the RNF 44 mcg ow treatment group, and 0.14 in the placebo treatment group). Although in the current study, conversion to CDMS was defined as either a second attack or a sustained increase (≥ 1.5 points) in the EDSS score, the CHMP considered that there was no clinically significant increase in disability progression during the course of the study for any of the treatment groups.

During their review, the CHMP expressed concerns with respect to the definition of 'high-risk patient' used in the study 27025. This study included patients with a single, first clinical event suggestive of MS and at least 2 clinically silent T2 lesions, with a size of at least 3 mm, at least one of which was ovoid or periventricular or infratentorial. The CHMP noted that the definition of 'high risk to conversion' is not well established. Based on prior studies with other interferon products for similar indications, a more conservative approach was previously applied, whereby patients with at least nine T2 hyperintense lesions on the initial scan and at least one new T2 or one new Gd-enhancing lesion on a follow-up scan have been referred to in the product information. In a prior study with Betaferon (BENEFIT), a higher risk for progression to CDMS within 2 years was seen in monofocal patients with at least 9 T2 lesions or Gd-enhancement on the brain MRI at baseline. The risk of CDMS in the placebo group for patients with these characteristics increased from 31% in patients with <9 T2 lesions to 55% in patients with ≥9 T2 lesions. Similarly, the risk of CDMS increased from 36% in patients without Gd-enhancing lesions to 63% in patients with Gd-enhancing lesions.

Similar trends were observed in the current study 27025. Placebo patients with ≥9 T2 lesions at baseline had an estimated 40% risk of developing CDMS over 2 years as compared with 32% of

patients with less than 9 lesions. Placebo patients with Gd-enhancing lesions at baseline had 46% risk of developing CDMS, compared with 31% of patients with no such lesions.

Similarly, placebo patients with ≥9 T2 lesions at baseline had an estimated 96% risk to develop McDonald MS over 2 years as compared with 62% of patients with less than 9 lesions. Placebo patients with Gd-enhancing lesions at baseline had 94% risk to develop McDonald MS, compared with 79% of patients with no such lesions. Considering these data, the CHMP was of the view that those patients with ≥9 T2 lesions at baseline and/or those patients with Gd-enhancing lesions at baseline could be seen as a population at highest risk of conversion within 2 years.

In the current study, statistically significant reductions in time to CDMS were only observed in those patients with ≥9 T2 lesions and/or presence of Gd-enhancing lesions at baseline, in both the 44 mcg tiw and ow dose groups. For time to McDonald MS, statistically significant effects were observed for all four subgroups, but only for the RNF 44 mcg tiw dose. The CHMP considered that positive trends were seen in all patient categories and the lack of statistical significance could be due to a lower number of subjects in some subgroups.

Overall, given the current data, the CHMP concluded that patients with ≥9 T2 at baseline and/or with Gd-enhancing lesions at baseline could be seen to be at highest risk of conversion within 2 years, and requested that the MAH revise the text in section 5.1 of the SmPC as follows:

"For the time being there is no well established definition of a high risk patient, although a more conservative approach is to accept at least nine T2 hyperintense lesions on the initial scan and at least one new T2 or one new Gd-enhancing lesion on a follow-up scan taken at least 1 month after the initial scan. In any case, treatment should only be considered for patients classified as high risk."

The CHMP considered that steroid treatment of the first event was not mandated by the protocol, but given at the discretion of the investigator. Overall, 365 out of 517 randomized subjects (71%) received steroids (i.v. in most cases) to treat the first clinical demyelinating event. Subjects who received steroids at baseline and who were allocated to placebo, RNF 44 mcg ow and RNF 44 mcg tiw had a cumulative probability of 86%, 74% and 65%, respectively of converting to McDonald MS, compared with 85%, 78% and 56%, of subjects who did not, respectively. Similarly, subjects receiving steroids and who were allocated to placebo, RNF 44 mcg ow and RNF 44 mcg tiw had a cumulative probability of 39%, 22% and 24%, respectively of converting to CDMS, compared with 34%, 21% and 12%, respectively who had not. The CHMP noted that the subgroup with no prior steroid therapy was relatively small (approximately 30% of the population), but considered that the data indicated a very similar magnitude of effect in both patient categories. In this context, the CHMP was of the opinion that intravenous steroid treatment need not be a mandatory component for selecting high-risk patients for treatment with Rebif. Thus, the CHMP concluded that restricting the indication to patients severe enough to warrant treatment with intravenous steroids was not necessary.

The CHMP considered that exploratory analyses were done comparing the two dosing regimens; these showed no statistically significant differences between the 44 mcg tiw and ow dose groups with respect to CDMS (p=0.774). However, the difference between the tiw and ow dose groups for time to McDonald MS was statistically significant (p=0.009). Furthermore, 44 mcg tiw was observed to statistically significantly reduce the mean number of CUA lesions per subject per scan (p=0.002) compared to 44 mcg ow.

Overall, the CHMP concluded that study 27075 has shown a benefit of treatment with Rebif in patients with CIS. Based on the current data this was most consistently shown for the 44 mcg tiw treatment group. The results were statistically significant for both time to McDonald MS (2005) and time to CDMS in those patient categories previously considered by CHMP as 'high risk', namely those patients with

≥9 T2 lesions and/or those patients with presence of Gd-enhancing lesions at baseline, and regardless of monofocal or multifocal disease presentation.

The rationale for the alternative 44 mcg ow dosing regimen was questioned by the CHMP. Although it was acknowledged that once-weekly dosing may enhance patient adherence to therapy, the CHMP was concerned that based on the data available, efficacy of this dosing regimen could be inferior to the thrice weekly treatment and requested that the MAH should further discuss the rationale for proposing a 44 mcg ow dose regimen from an efficacy and safety/tolerability point of view. Eventually, the MAH took the decision not to pursue the once-weekly posology in the current procedure. Consequently, the Type IB variation to introduce additional pack sizes for the PFP and PFS initiation packs, relevant to the once weekly dosing, was no longer needed and therefore, the MAH withdrew the type IB variation.

Clinical safety

Patient exposure

The double blind (DB) safety population consisted of all randomized subjects who received at least one dose of study drug. A subpopulation, referred to as the "OL safety population" consisted of all subjects from the DB safety population who received at least one open label study treatment injection with RNF 44 mcg tiw after having converted to CDMS. The DB Safety Population included 515 subjects, 171 subjects in the placebo treatment group, 173 in the RNF 44 mcg ow group and 171 in the RNF 44 mcg tiw group (see section Participant flow).

A total of 130 subjects converted to CDMS and of these, 120 subjects (59 in the placebo treatment group, 30 in the RNF 44 mcg ow group and 31 in the RNF 44 mcg tiw group) switched to OL RNF 44 mcg tiw and were included in the OL safety population. A descriptive summary of the safety population is provided in table 2.

Demographic characteristics of subjects in the DB safety population were balanced across treatment groups and similar to the ITT population.

Treatment exposure

Table 9 summarises the study drug exposure during the DB treatment period (up to 24 months or conversion to CDMS, whichever occurred first). The mean time on treatment was slightly lower in the placebo treatment group (533.1 days) as compared to the active treatment groups (604.0 days in the RNF 44 mcg tiw treatment group and 609.5 days in the RNF 44 mcg ow treatment group). This was consistent with the higher CDMS conversion rate in the placebo treatment group as compared to both active treatment groups. Treatment exposure during the OL period was similar between the treatment groups (initial placebo, initial RNF 44 mcg ow and initial RNF mcg tiw).

Table 9: Exposure to DB Treatment (DB Safety Population)

Characteristic	Statistics	Placebo (n=171)	RNF 44 mcg ow (n=173)	RNF 44 mcg tiw (n=171)
Time on Treatment during the DB Period (Days) [a]	n (missing)	171 (0)	173 (0)	171 (0)
	Mean (SD)	533.1 (236.2)	609.5 (213.2)	604.0 (212.5)
	Median	714.0	719.0	720.0
	Q1; Q3	283.0; 722.0	648.0; 724.0	569.0; 724.0
	Min; Max	10; 745	1; 743	21; 746

(a) Time on treatment during the DB period is defined as the date of the last DB study treatment injection minus the date of the first DB study treatment injection plus one.

Source: refer to Table 15-70 in the Study 27025 CTR

Adverse events

A summary of the incidence of treatment-emergent adverse events (TEAEs) for the DB and OL treatment periods is provided in tables 10 and 11, respectively.

Table 10: Incidence of TEAEs during DB Treatment Period (DB Safety Population)

Characteristic	Placebo (n=171) n (%)	RNF 44 mcg ow (n=173) n (%)	RNF 44 mcg tiw (n=171) n (%)
Any TEAE[a]	134 (78.4)	158 (91.3)	149 (87.1)
Any drug-related TEAE[a][b]	74 (43.3)	141 (81.5)	133 (77.8)
Any TEAE[a] of severe intensity	9 (5.3)	8 (4.6)	11 (6.4)
Any serious TEAE[a]	12 (7.0)	8 (4.6)	6 (3.5)
Any TEAE[a] leading to death	2 (1.2)	0 (0.0)	0 (0.0)
Any TEAE[a] leading to study treatment discontinuation	6 (3.5)	4 (2.3)	5 (2.9)

TEAE = Treatment-Emergent Adverse Event.

(a) During the DB treatment period.

(b) Probable or possible relationship with study treatment according to investigator.

Source: refer to Table 15-179 in the Study 27025 CTR

Table 11: Incidence of TEAEs during OL Treatment Period (OL Safety Population)

Characteristic	Initial Placebo/ OL RNF 44 mcg tiw (n=59) n (%)	Initial RNF 44 mcg ow/ OL RNF 44 mcg tiw (n=30) n (%)	Initial RNF 44 mcg tiw/ OL RNF 44 mcg tiw (n=31) n (%)
Any TEAE[a]	47 (79.7)	20 (66.7)	20 (64.5)
Any drug-related TEAE[a][b]	37 (62.7)	14 (46.7)	18 (58.1)
Any TEAE[a] of severe intensity	1 (1.7)	2 (6.7)	3 (9.7)
Any serious TEAE[a]	1 (1.7)	0 (0.0)	1 (3.2)
Any TEAE[a] leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Any TEAE[a] leading to study treatment discontinuation	1 (1.7)	1 (3.3)	2 (6.5)

TEAE = Treatment-Emergent Adverse Event.

(a) During the OL treatment period.

(b) Probable or possible relationship with study treatment according to investigator.

Source: refer to Table 15-197 in the Study 27025 CTR

The incidences of the most common TEAEs (preferred terms) during the DB and OL treatment periods are summarized in Tables 12 and 13, respectively.

Table 12: Incidence of Most Common TEAEs during DB Treatment Period (≥10% of subjects in DB Safety Population)

Preferred Term	Placebo (n=171) n (%)	RNF 44 mcg ow (n=173) n (%)	RNF 44 mcg tiw (n=171) n (%)
Subjects with most common events			
Influenza like illness	34 (19.9)	122 (70.5)	93 (54.4)
Headache	46 (26.9)	37 (21.4)	46 (26.9)
Injection site erythema	3 (1.8)	34 (19.7)	50 (29.2)
Nasopharyngitis	22 (12.9)	23 (13.3)	17 (9.9)
Upper respiratory tract infection	20 (11.7)	13 (7.5)	17 (9.9)
Pyrexia	9 (5.3)	22 (12.7)	6 (3.5)

MedDRA dictionary version 13.0.

Source: refer to Table 15-193 in the Study 27025 CTR

Table 13: Incidence of Most Common TEAEs during OL Treatment Period (≥10% of Subjects in OL Safety Population)

Preferred Term	Initial Placebo/ OL RNF 44 mcg tiw (n=59) n (%)	Initial RNF 44 mcg ow/ OL RNF 44 mcg tiw (n=30) n (%)	Initial RNF 44 mcg tiw/ OL RNF 44 mcg tiw (n=31) n (%)
Subjects with most common events			
Influenza like illness	24 (40.7)	3 (10.0)	8 (25.8)
Injection site erythema	13 (22.0)	3 (10.0)	4 (12.9)
Alanine aminotransferase increased	3 (5.1)	3 (10.0)	3 (9.7)
Leukopenia	2 (3.4)	3 (10.0)	3 (9.7)
Fatigue	2 (3.4)	1 (3.3)	4 (12.9)
Thrombocytopenia	1 (1.7)	3 (10.0)	1 (3.2)
Hypertension	1 (1.7)	3 (10.0)	0 (0.0)

MedDRA dictionary version 13.0.

Source: refer to Table 15-210 in the Study 27025 CTR

During the blinded treatment period, the RNF treatment groups showed an AE pattern as expected for IFN beta-1a, with a higher incidence of AEs such as influenza-like illness, pyrexia and injection site erythema than placebo. The injection site erythema AEs occurred more frequently in the RNF 44 mcg tiw group than in the 44 mcg ow group. The incidence of influenza like illness and pyrexia was slightly higher for the RNF 44 mcg ow group than the 44 mcg tiw group. Most AEs across the treatment groups were mild or moderate in intensity.

AEs of special interest

Adverse events of interest with interferon-beta-1a treatment included the following pre-specified groups: flu-like syndrome, cytopenia, hepatic disorders, thyroid disorders, hypersensitivity reactions, skin rashes, depression and suicidal ideation and injection site reactions. The incidence of these events is summarized in table 14.

Table 14: Incidence of Pre-specified AEs during DB Treatment Period (≥1% of Subjects)

Pre-Specified Group Preferred Term	Placebo (n=171)	RNF 44 mcg ow (n=173)	RNF 44 mcg tiw (n=171)
Cytopenia	4 (2.3%)	9 (5.2%)	19 (11.1%)

Table 14: Incidence of Pre-specified AEs during DB Treatment Period (≥1% of Subjects)

Pre-Specified Group Preferred Term	Placebo (n=171)	RNF 44 mcg ow (n=173)	RNF 44 mcg tiw (n=171)
Leukopenia	2 (1.2%)	4 (2.3%)	7 (4.1%)
Lymphopenia	1 (0.6%)	1 (0.6%)	3 (1.8%)
Neutropenia	1 (0.6%)	6 (3.5%)	13 (7.6%)
Thrombocytopenia	1 (0.6%)	0 (0)	5 (2.9%)
Depression and Suicidal Ideation	14 (8.2%)	11 (6.4%)	14 (8.2%)
Depressed mood	2 (1.2%)	2 (1.2%)	0 (0)
Depression	10 (5.8%)	9 (5.2%)	14 (8.2%)
Flu-like Syndrome	34 (19.9%)	122 (70.5%)	93 (54.4%)
Influenza-like illness	34 (19.9%)	122 (70.5%)	93 (54.4%)
Hepatic Disorders	8 (4.7%)	16 (9.2%)	19 (11.1%)
Alanine aminotransferase increased	5 (2.9%)	11 (6.4%)	14 (8.2%)
Aspartate aminotransferase increased	3 (1.8%)	9 (5.2%)	10 (5.8%)
Hepatic enzyme increased	1 (0.6%)	1 (0.6%)	3 (1.8%)
Hypersensitivity Reactions	11 (6.4%)	10 (5.8%)	16 (9.4%)
Dermatitis allergic	1 (0.6%)	1 (0.6%)	2 (1.2%)
Erythema	1 (0.6%)	0 (0)	5 (2.9%)
Oedema peripheral	1 (0.6%)	3 (1.7%)	0 (0)
Pruritus generalized	0 (0)	1 (0.6%)	2 (1.2%)
Rash	3 (1.8%)	4 (2.3%)	2 (1.2%)
Rash pruritic	0 (0)	0 (0)	2 (1.2%)
Urticaria	1 (0.6%)	0 (0)	2 (1.2%)
Injection Site Reaction	12 (7.0%)	42 (24.3%)	61 (35.7%)
Injection site erythema	3 (1.8%)	34 (19.7%)	50 (29.2%)
Injection site hematoma	3 (1.8%)	6 (3.5%)	8 (4.7%)
Injection site infection	0 (0)	0 (0)	2 (1.2%)
Injection site oedema	0 (0)	1 (0.6%)	2 (1.2%)
Injection site pain	6 (3.5%)	4 (2.3%)	8 (4.7%)
Injection site rash	0 (0)	0 (0)	3 (1.8%)
Skin Rashes	9 (5.3%)	8 (4.6%)	16 (9.4%)
Dermatitis allergic	1 (0.6%)	1 (0.6%)	2 (1.2%)
Erythema	1 (0.6%)	0 (0)	5 (2.9%)
Pruritus generalized	0 (0)	1 (0.6%)	2 (1.2%)
Rash	3 (1.8%)	4 (2.3%)	2 (1.2%)
Rash pruritic	0 (0)	0 (0)	2 (1.2%)
Urticaria	1 (0.6%)	0 (0)	2 (1.2%)
Thyroid Disorders	2 (1.2%)	5 (2.9%)	11 (6.4%)
Anti-thyroid antibody positive	1 (0.6%)	1 (0.6%)	2 (1.2%)
Autoimmune thyroiditis	1 (0.6%)	0 (0)	2 (1.2%)
Goiter	0 (0)	2 (1.2%)	1 (0.6%)
Hyperthyroidism	0 (0)	2 (1.2%)	1 (0.6%)
Hypothyroidism	0 (0)	0 (0)	3 (1.8%)
Tri-iodothyronine increased	0 (0)	0 (0)	2 (1.2%)

Source: Assessor's table, extracted from Table 12-6 of the CSR for Study 27025.

Increased incidence of AEs related to IFN beta-1a treatment was observed in the RNF 44 mcg treatment groups as compared to placebo.

A similar analysis for the OL treatment showed an increased incidence of flu-like illness and injection site reactions in newly exposed subjects (those subjects initially in the placebo group), which was considered expected by the CHMP.

Serious adverse events

Two deaths occurred during the study, both in the placebo group during the DB treatment period (one patient with a history of cholecystolithiasis died of severe acute pancreatic necrosis and one patient died due to fatal hematoma after surgery for subtotal excision of glioblastoma).

Serious adverse events (SAEs) other than the two fatal events were reported in 12 subjects (7.0%) in the placebo treatment group, 8 subjects (4.6%) in the RNF 44 mcg ow group and 6 subjects (3.5%) in the RNF 44 mcg tiw group.

There were 6 subjects in the RNF 44 mcg tiw group with one or more SAEs (other than death) that occurred during the DB treatment period, including cases of appendicitis (3), dermoid cyst (1), tonsillitis (1), drug hypersensitivity (1), deafness congenital (1) and acute myocardial infarction (1). There were 8 subjects in the RNF 44 mcg ow group that experienced one or more SAEs: spontaneous abortion (1), hypacusis (1), cervical polyp (1), varicella (1), nasal septum deviation (1), iron deficiency anemia (1), tibia fracture (1), muscle rupture (1) and tonsillar disorder (1).

These SAEs were either assessed unlikely to be related or unrelated to the IMP by the MAH, the CHMP also considered a possible relationship to Rebif in these cases unlikely.

SAEs assessed as possibly related to study drug included a case of varicella in one subject treated with RNF 44 mcg ow and 2 spontaneous abortions, one in a subject receiving placebo and one in a subject receiving RNF 44 mcg ow.

The SAE of varicella concerned a 26-year-old female with a history of varicella infection. She developed symptoms of varicella approximately 20 weeks after starting treatment with RNF 44 mcg ow. She received treatment with acyclovir and the event was considered resolved within a week. According to the narrative, a search of the safety database identified other confirmed reports of varicella infection/herpes zoster/shingles in patients treated with Rebif (with lack of clarity as to whether this includes any cases of primary infection).

In the OL period, SAEs were reported in one subject initially randomized to placebo (brief psychotic disorder) and one subject initially randomized to RNF 44 mcg tiw (cholelithiasis). Both events were assessed as unrelated to the study drug by the investigator.

Discontinuation due to adverse events

During the DB treatment period, 6 subjects (3.5%) in the placebo treatment group, 4 subjects (2.3%) in the RNF 44 mcg ow treatment group and 5 subjects (2.9%) in the RNF 44 mcg tiw treatment group permanently discontinued treatment due to a TEAE. Two additional subjects in the placebo treatment group discontinued due to pregnancy.

The most common reason for discontinuation was influenza-like illness (2 subjects each in the RNF 44 mcg ow and 44 mcg tiw group). One subject in the 44 mcg tiw group was discontinued due to mild increase in liver transaminases considered possibly related to study drug.

During the OL treatment period, three subjects permanently discontinued treatment because of increase in ALT and AST, one in each treatment group. In addition, one subject initially treated with

RNF 44 mcg tiw discontinued treatment permanently due to injection site pain. One subject in the initial placebo group switching to RNF tiw discontinued treatment due to pregnancy.

Laboratory findings

Most laboratory parameters remained within the normal range during the DB treatment period.

Haematology

The majority of worst post-baseline CTCAE grades in the DB treatment period for each of the haematology assessments were Grade 0 or 1 for all treatment groups. The most notable toxicity shifts were seen for haemoglobin, WBC count, neutrophils and lymphocytes. There was a greater frequency of Grade 2 and Grade 3 toxicity for WBC count, neutrophils and lymphocytes in the two RNF treatment groups compared with the placebo group. One Grade 4 shift was observed in the placebo group for neutrophils in a subject with a normal baseline value. No Grade 4 toxicities were observed in the RNF treatment groups.

Biochemistry

The majority of the worst post-baseline CTCAE toxicity grades in the DB treatment period for each of the biochemistry assessments were Grade 0 or 1 for all treatment groups. The most notable toxicity shifts were reported for total bilirubin, AST and ALT.

In the placebo group, there was one case of Grade 2 toxicity for total bilirubin in a subject who had a normal value at baseline. Two subjects with normal baseline values and one subject with Grade 1 baseline value shifted to Grade 2 toxicity for AST. Six subjects with normal baseline values and one subject with Grade 1 baseline value shifted to Grade 2 toxicity for ALT and 1 subject with normal baseline value developed Grade 3 toxicity.

In the RNF 44 mcg ow group, a shift to Grade 2 toxicity for total bilirubin occurred in one subject with normal baseline value and one subject with Grade 1 baseline value. Five subjects with normal baseline values shifted to Grade 2 toxicity for AST. Seven subjects with normal baseline values and three subjects with Grade 1 baseline values shifted to Grade 2 toxicity for ALT, whereas five subjects with normal baseline values and one subject with Grade 1 baseline values shifted to Grade 3 toxicity.

In the RNF 44 mcg tiw group, thirteen subjects with normal baseline values shifted to Grade 2 toxicity for AST and two subjects shifted to Grade 3. Nineteen subjects with normal baseline values and three subjects with Grade 1 baseline values shifted to Grade 2 toxicity for ALT. Eight subjects with normal baseline values and three subjects with Grade 1 baseline values shifted to Grade 3. A shift from normal to Grade 4 toxicity was reported for one subject.

Overall, haematology parameters such as haemoglobin, platelets, WBC counts, lymphocyte counts and neutrophil counts were lower in both active treatment groups compared with the placebo group, generally with a dose dependent decrease. The RNF 44 mcg tiw treatment regimen showed a higher frequency of abnormally high AST and ALT values compared with the RNF 44 mcg ow regimen.

Immunogenicity

Samples for immunogenicity assessments were taken at 6-monthly intervals. No sampling was performed at conversion to CDMS (at the end of the DB Period). The same ELISA for binding antibodies (BAbs) and the same cell-based assay for the determination of neutralizing anti-interferon-beta antibodies (NAbs), i.e. the cytopathic effect (CPE) assay that was used for previous Rebif studies, was used in study 27025.

All samples were screened for BAbs and BAb positive samples were further tested for NAbs, as the ELISA test for BAbs was found to be an effective screening procedure for NAbs. NAb positivity was defined by a titer of ≥20 NU/ml.

Twenty-five (14.8%) subjects treated with RNF 44 mcg tiw were NAb-positive at the Last Observed Visit (LOV) of the 24-month study period. The proportion of subjects treated with RNF 44 mcg tiw who were NAb-positive at any time during the 24 months was 15.4%; the median NAb titer was 1345 NU/ml. Twenty-eight (16.7%) subjects treated with RNF 44 mcg ow were NAb-positive at the LOV of the whole study period. The proportion of subjects treated with RNF 44 mcg ow who were NAb-positive at any time during the 24 months was 18.5%; the median NAb titer was 393 NU/ml.

The CHMP considered that similar NAb-positive rates were observed with ow and tiw dosing, at a frequency in line with that previously observed with RNF treatment. Median titers were lower with the 44 mcg ow treatment. Antibody formation will be further followed in an extension study, which the CHMP considered of interest with regard to long-term efficacy and safety.

4.2.4. Discussion of clinical safety

The CHMP considered that during the blinded treatment period, the RNF treatment groups showed an AE pattern as could be expected of interferon beta-1a, with a higher incidence of adverse events such as influenza-like illness, pyrexia and injection site erythema compared to placebo.

In the context of varicella reports identified in the MAH´s safety database, the CHMP requested that the MAH discuss whether 'varicella infection' and/or 'herpes zoster' should be included in section 4.8 of the SmPC. In response to this request, the MAH provided a cumulative review and a detailed analysis of herpes zoster and varicella Infection cases. The CHMP was of the opinion that the review did not indicate an increased risk of herpes zoster/ varicella in MS patients treated with Rebif and agreed that the company will continue to monitor these cases as part of the routine pharmacovigilance activities.

The CHMP considered that the incidence of injection site erythema AEs, as well as laboratory abnormalities such as elevated liver transaminases was slightly lower in the RNF 44 mcg ow group than in the 44 mcg tiw group, whereas the incidence of influenza-like illness and pyrexia was slightly higher. Over the double-blind period of study 27025, the proportion of patients experiencing flu-like symptoms at any time was 70.5% in the RNF 44 mcg ow group compared with 54.4% in the RNF 44 mcg tiw group. Similarly, 12.7% of patients in the 44 mcg ow group experienced pyrexia, compared with 3.5% in the tiw group. The CHMP considered that this could be a random finding or, as discussed by the MAH, the difference in incidence could be explained by the more sustained level of IFN-beta effect with fewer peaks and troughs in the tiw compared with the ow dosing. As mentioned in the clinical efficacy section, the alternative ow dosing regimen was withdrawn by the MAH during the procedure and thus, the CHMP agreed that this observation did not need to be discussed further.

From a safety perspective, the CHMP concluded that the overall safety and tolerability profile for Rebif was as expected and did not lead to any new safety concerns.

4.3. Risk management plan

The CHMP, having considered the data submitted in the dossier, was of the opinion that no new pharmacovigilance activities in addition to those already being performed were needed to monitor the safety of the product.

With this procedure, the opportunity was taken to introduce the standard text regarding the risk management plan submission requirements in the Annex II.

4.4. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed (new text= underlined, deleted text= strikethrough). The changes shown below are those related to the extension of indication, for a complete set of changes see Attachment 1 to this report.

Summary of Product Characteristics

Section 4.1

Rebif is indicated for the treatment of

- patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis (see section 5.1)

- patients with relapsing multiple sclerosis. In clinical trials, this was characterised by two or more acute exacerbations in the previous two years (see section 5.1).

Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapsing activity (see section 5.1).

Section 4.2

Posology

...

First demyelinating event

The posology for patients who have experienced a first demyelinating event is 44 micrograms of Rebif given three times per week by subcutaneous injection.

Section 4.8

...

The data ~~presented is~~are obtained from ~~pooled~~ controlled clinical studies in multiple sclerosis ~~(placebo=824 patients; Rebif 22 micrograms three times per week (TIW)=398 patients; Rebif 44 micrograms TIW=727 patients)~~ and show~~s~~ the frequency of adverse reactions ~~observed at six months (~~in excess over placebo). Adverse reactions are listed below by frequency of occurrence and by MedDRA System Organ Class.

Section 5.1

Single clinical event suggestive of multiple sclerosis

One 2-year controlled clinical trial with Rebif was performed in patients with a single clinical event suggestive of demyelination due to multiple sclerosis. The patients enrolled into the trial had at least two clinically silent lesions on the T2-weighted MRI scan, with a size of at least 3 mm, at least one of which is ovoid or periventricular or infratentorial. Any disease other than multiple sclerosis that could better explain signs and symptoms of the patient had to be excluded.

Patients were randomised in a double-blind manner to either Rebif 44 micrograms given three times per week, Rebif 44 micrograms once weekly, or placebo. If a second clinical demyelinating event

occurred confirming definite multiple sclerosis, patients switched to the recommended posology of Rebif 44 micrograms three times per week in an open label manner, while maintaining blinding as to initial randomisation. Efficacy results of Rebif 44 micrograms given three times per week compared to placebo from this study are as follows:

Parameter Statistics	**Treatment**		**Treatment Comparison Rebif 44 mcg tiw versus Placebo**		
	Placebo (n=171)	**Rebif 44 mcg tiw* (n=171)**	**Risk Reduction**	**Cox's Proportional Hazard Ratio [95% CI]**	**Log-Rank p-value**
McDonald (2005) Conversion					
Number of events	144	106	51%	0.49 [0.38;0.64]	<0.001
KM Estimate	85.8%	62.5%			
CDMS Conversion					
Number of events	60	33	52%	0.48 [0.31;0.73]	<0.001
KM Estimate	37.5%	20.6%			
Mean CUA Lesions per Subject per Scan During the Double Blind Period					
Least Square Means (SE)	2.58 (0.30)	0.50 (0.06)	81%	0.19 [0.14;0.26]	<0.001
* tiw – three times per week					

For the time being there is no well established definition of a high risk patient, although a more conservative approach is to accept at least nine T2 hyperintense lesions on the initial scan and at least one new T2 or one new Gd-enhancing lesion on a follow-up scan taken at least 1 month after the initial scan. In any case, treatment should only be considered for patients classified as high risk.

Package Leaflet

Section 1

Rebif is used for the treatment of multiple sclerosis. It has been shown to reduce the number and the severity of relapses and to slow the progression of disability. It is also approved for use in patients who have experienced a single clinical event likely to be a first sign of multiple sclerosis.

Section 3

Dose

Patients who have experienced a single clinical event

The usual dose is 44 micrograms (12 million IU) given three times per week for adults and adolescents from 16 years of age.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of the Slovak Republic, Slovenia, Norway and Romania.

5. Overall conclusion and impact on the benefit/risk balance

Overall, the CHMP was of the view that results of study 27075 supported a positive benefit-risk balance of Rebif in the treatment in patients with clinically isolated syndrome to delay a diagnosis of multiple sclerosis. Based on the available data, this was most consistently observed with the 44 mcg tiw (three times a week) treatment group. The results were statistically significant for both time to McDonald MS (2005) and time to CDMS in those patient categories previously considered by CHMP as 'high risk', namely those patients with ≥9 T2 lesions and/or those patients with presence of Gd-enhancing lesions at baseline and regardless of the monofocal or multifocal disease presentation. From a safety perspective, the overall safety and tolerability profile of Rebif was as expected and did not lead to any new safety concerns.

In conclusion, the submitted data were considered to support the following indication:

"Rebif is indicated for the treatment of patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis (see section 5.1).

Section 5.1

...

For the time being there is no well established definition of a high risk patient, although a more conservative approach is to accept at least nine T2 hyperintense lesions on the initial scan and at least one new T2 or one new Gd-enhancing lesion on a follow-up scan taken at least 1 month after the initial scan. In any case, treatment should only be considered for patients classified as high risk."

The CHMP noted that the MAH is conducting an extension study REFLEXION, a double-blind extension of the study 27025 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 multiple sclerosis, treated with Rebif New Formulation. The CHMP was of the view that this extension study could provide additional comparative data on the long-term efficacy and safety of both dosing regimens (tiw and ow) and recommended that these be submitted for review once available.

With respect to the Type IB variation initially submitted in a group with the Type II variation – extension of indication, the CHMP concluded that the approval of the additional pack sizes was linked to the approval of the 44 mcg once weekly dosing regimen. Since the MAH decided not to pursue the alternative ow dosing regimen, the above mentioned type IB variation was withdrawn at the time of response to the Request for Supplementary Information and the evaluation procedure was finalised accordingly (see section 6 - Recommendations).

6. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type
C.I.6 a)	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication: Update of sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and sections 1 and 3 of the Package Leaflet to include information on a new indication, i.e. treatment of patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis. These updates affect the PI of the 44 mcg presentations (pre-filled syringe, pre-filled pen and cartridges) and the PI of the initiation pack presentations (pre-filled syringe, pre-filled pen and cartridges). In addition, minor editorial changes were implemented across the SmPC and the Package leaflet, and the DDPS version number was removed from Annex II. Furthermore, Annex II was updated to introduce the standard text regarding the risk management system. The MAH also took the opportunity to update the list of local representatives in the Package Leaflet.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Conditions and requirements of the marketing authorisation

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

PSURs

The MAH will submit PSURs on an annual basis until otherwise specified.

7. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication: Update of sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and sections 1 and 3 of the Package Leaflet to include information on a new indication, i.e. treatment of patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis. These updates affect the PI of the 44 mcg presentations (pre-filled syringe, pre-filled pen and cartridges) and the PI of the initiation pack presentations (pre-filled syringe, pre-filled pen and cartridges). In addition, minor editorial changes were implemented across the SmPC and the Package leaflet and the DDPS version number was removed from Annex II. Furthermore, Annex II was updated to introduce the standard text regarding the risk management system. The MAH also took the opportunity to update the list of local representatives in the Package Leaflet.

Summary

The revised CHMP variation assessment report will be published as part of the EPAR, following review/ deletion of confidential information.