



UNIVERSITY OF THESSALY
School of Medicine



NET-MS

2011

An expert information system which has been developed to identify whether certain treatments in Multiple Sclerosis (MS) are associated with better outcome in terms of efficacy and safety

<http://netms.med.uth.gr>

LARISSA, 2011

FAQs and Users' manual

(1) What is NET-MS?

(2) How NET-MS is being used?

(3) More

(1) What is NET-MS?

NET-MS is an expert information system which has been developed to identify whether certain treatments in Multiple Sclerosis (MS) are associated with better outcome in terms of efficacy and safety.

1a. Why should a network system be useful?

For a given clinical indication, clinicians and healthcare policy makers often have to choose between different active interventions (treatments). Many competing treatments have not been directly (head-to-head) compared in randomized controlled trials RCTs. Even when different interventions have been directly compared in RCTs such evidence is often limited and insufficient. This lack of evidence from direct comparison between the alternative treatments makes the decision of choosing a treatment difficult. Because of the lack of direct evidence, indirect comparisons have been recommended and used for evaluating the efficacy of alternative treatments.

1b. What NET-MS provides to the clinicians?

NET- MS provides the clinician the following:

- a) An updated catalogue with all published RCTs in MS for a specific treatment with information regarding the primary outcomes, safety, demographic and prognostic factors.
- b) Direct comparisons' data (data synthesis) for every possible treatment combinations available by synthesizing pre-existing published evidence.

- c) Indirect comparisons' data (including data synthesis) integrating data from direct and indirect comparisons which strengthens the power of evidence.

1c. Why is indirect analysis helpful?

When there is no direct comparison, then the statistical methodology of multiple-treatments (network) meta-analysis may be applied to obtain some direct evidence of the relative efficacy of competing interventions, although the results of any indirect comparisons should be interpreted with great caution. The network meta-analysis methodology will allow: i) to synthesize the pre-existing published evidence, ii) to integrate data from direct and indirect comparisons and iii) to assess the strength and consistency of the evidence.

When the direct comparison is available, the indirect comparison is still useful: it provides more evidence. If there is no significant discrepancy in the results between the direct and indirect comparisons, the two results could be combined to obtain a more precise estimate. If there is significant discrepancy between the direct and indirect comparison, the validity of RCTs should be checked to investigate potential causes of discrepancy. A significant discrepancy between the direct and indirect comparison may be due to invalid result of the direct comparison, and /or the invalid results of the RCTs used in the indirect comparison.

1d. Which studies were excluded?

- All non RCTs were excluded.
- All studies with results for treatment on acute relapse were also excluded.
- Cross-over studies which did not provide data for each period separately were also excluded. If cross-over studies did provide data from each study period separately, only data from first period were included in the analysis.
- Studies comparing different administration ways of the same drug or studies comparing different formulation of the same drug were excluded. Follow up period data and extension period data of RCTs were excluded.
- Post-hoc analysis and retrospective analysis data were not included.
- If an RCT was published in more than one article, the data provided in the final analysis were only included.

-If in a study, patients with different MS type were included and data for each MS type were provided, these were reported as separate studies.

1e. Which outcomes were reported?

Binary outcomes were preferred.

Efficacy, which is clinicians' major concern, was tested in the 3 basic parameters:

1. Relapse
2. Disease progression
3. MRI lesions.

Safety results were also reported regarding

1. Adverse Events
2. Serious Adverse Events

Efficacy outcomes

1. Relapse: relapse free patients' data given in RCTs were used in NET-MS analyses.
2. Disease progression: Patients without disease progression were used in NET-MS analyses. EDSS score was the basic score preferred, with which patients were diagnosed to have progression.
3. MRI lesions: Patients without MRI lesions progression (all types of MRI lesions) were used in NET-MS. If an RCT provide data for MRI progression from more than one MRI lesions type, T2 lesions data were preferred.

Safety outcomes

1. Adverse Events: patients with Adverse Events data were reported.
2. Serious Adverse Events: patients with Serious Adverse Events were reported.

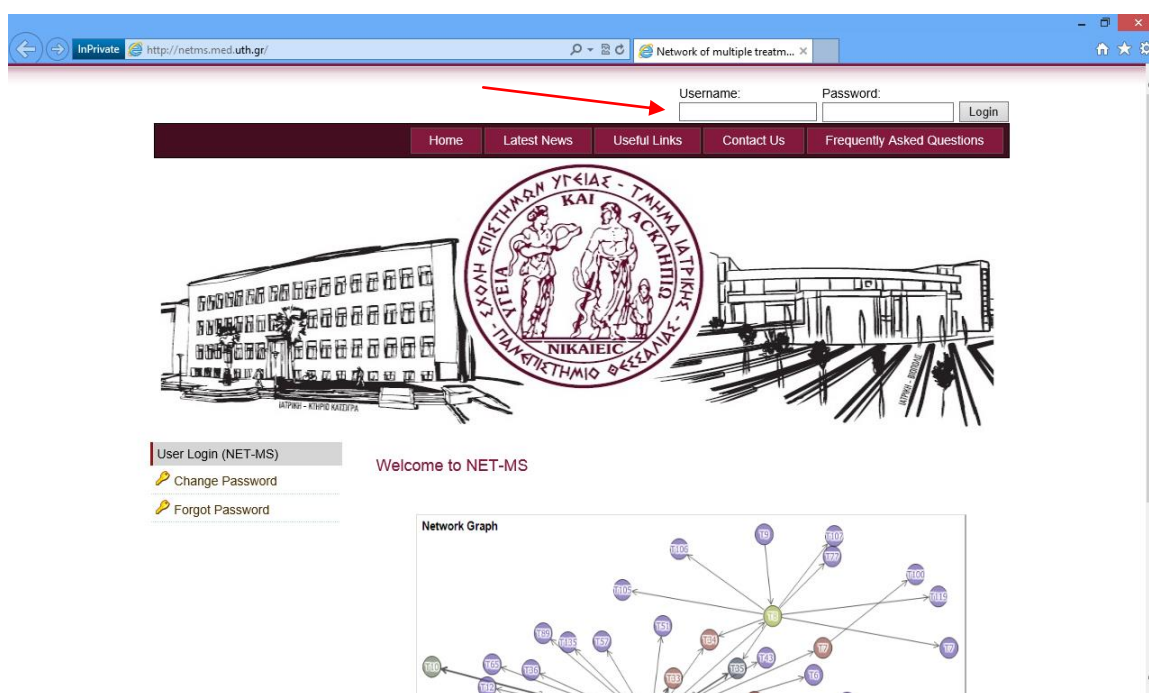
(2) How NET-MS is being used?

A unique username and password is provided to the users. Only clinicians have access to the NET-MS. For this reason there is no option for account creation on the web site.

NET-MS is easy to use following next steps.

It is mandatory to go in a consecutive way through steps 1 >2>3>4.

1. Login to the site





2. Choose an outcome (it is mandatory to be chosen before choose treatment of interest)

Browser address bar: <http://netms.med.uth.gr/default.aspx?id=2788BEC7-EC41-4F05-BD04-06D1383DAD67>

Network of multiple treatm...

Logout

Home NET-MS Latest News Useful Links Contact Us Frequently Asked Questions

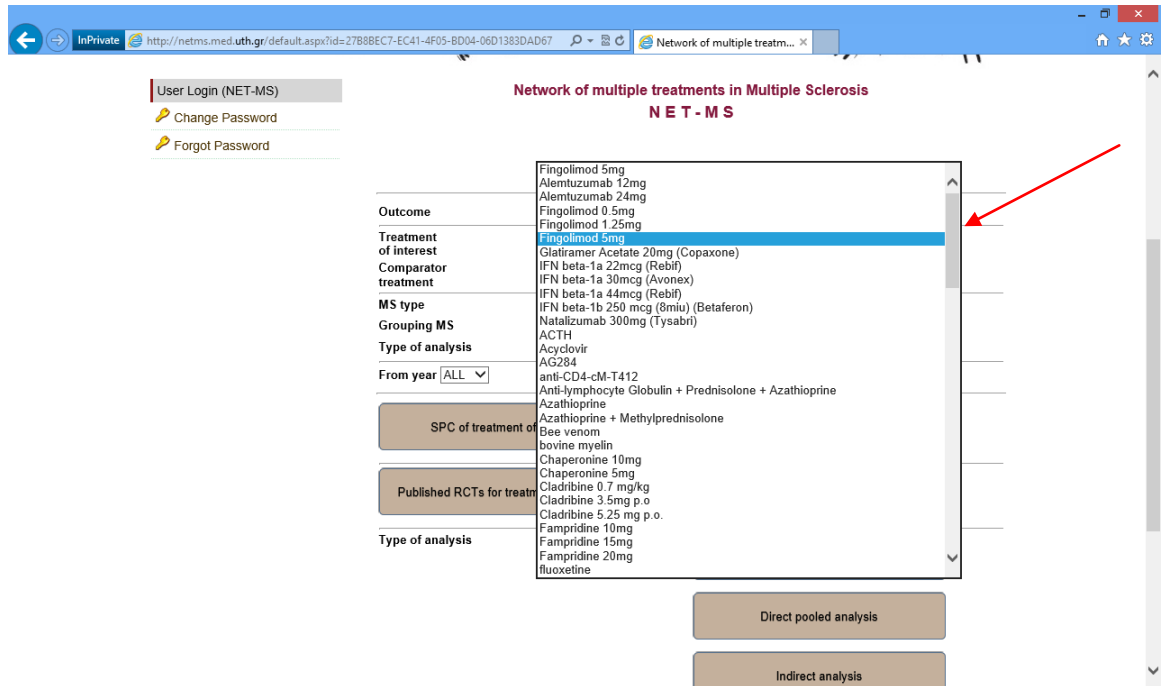


Network of multiple treatments in Multiple Sclerosis
NET - M S

User Login (NET-MS)
Change Password
Forgot Password

Outcome	(Choose outcome)
Treatment of interest	Patients with adverse events
Comparator treatment	Patients without disease progression
	Patients without MRI progression
	Relapse free patients
MS type	ALL
Grouping MS	ALL
Type of analysis	ALL

3. Choose a treatment of interest from the list provided



Network of multiple treatments in Multiple Sclerosis
NET - MS

User Login (NET-MS)
Change Password
Forgot Password

Outcome
Treatment of interest
Comparator treatment
MS type
Grouping MS
Type of analysis
From year ALL

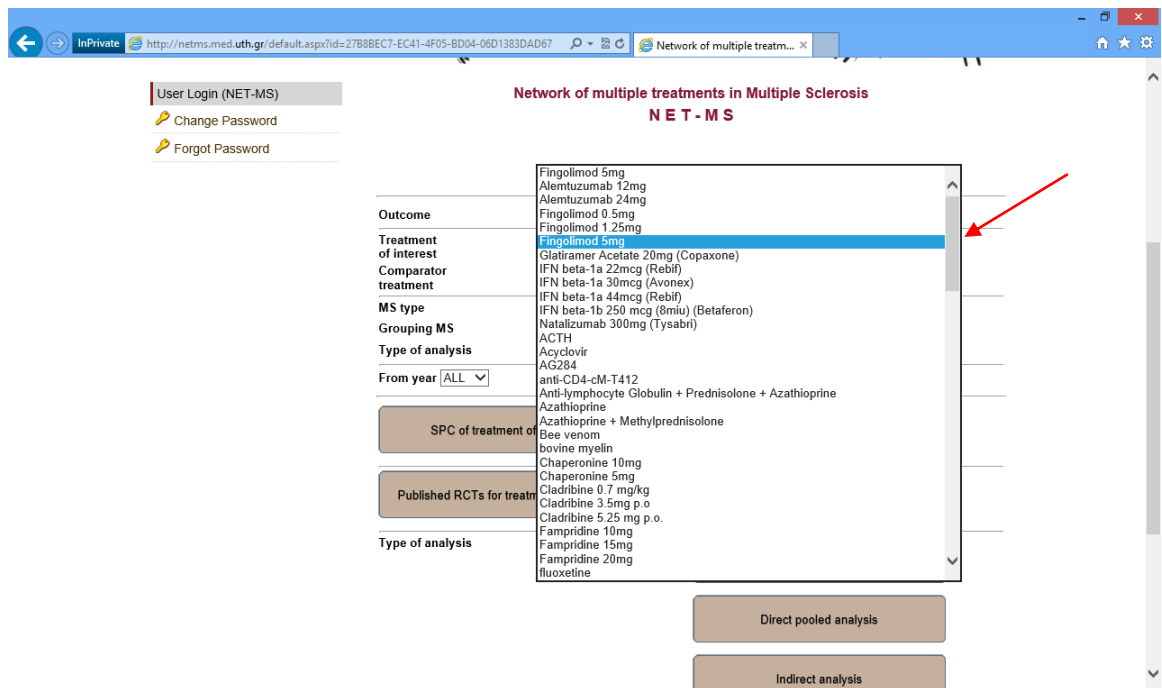
SPC of treatment of interest
Published RCTs for treatment of interest

Type of analysis

Direct pooled analysis
Indirect analysis

Fingolimod 5mg
Alemtuzumab 12mg
Alemtuzumab 24mg
Fingolimod 0.5mg
Fingolimod 1.25mg
Fingolimod 5mg
Glatiramer Acetate 20mg (Copaxone)
IFN beta-1a 22mcg (Rebif)
IFN beta-1a 30mcg (Avonex)
IFN beta-1a 44mcg (Rebif)
IFN beta-1b 250 mcg (8mlu) (Betaferon)
Natalizumab 300mg (Tysabri)
ACTH
Acyclovir
AG284
anti-CD4-cM-T412
Anti-lymphocyte Globulin + Prednisolone + Azathioprine
Azathioprine
Azathioprine + Methylprednisolone
Bee venom
bovine myelin
Chaperonline 10mg
Chaperonline 5mg
Cladribine 0.7 mg/kg
Cladribine 3.5mg p.o.
Cladribine 5.25 mg p.o.
Fampridine 10mg
Fampridine 15mg
Fampridine 20mg
fluoxetine

4. Choose a comparator treatment from the list provided



Network of multiple treatments in Multiple Sclerosis
NET - MS

User Login (NET-MS)
Change Password
Forgot Password

Outcome
Treatment of interest
Comparator treatment
MS type
Grouping MS
Type of analysis
From year ALL

SPC of treatment of interest
Published RCTs for treatment of interest

Type of analysis

Direct pooled analysis
Indirect analysis

Fingolimod 5mg
Alemtuzumab 12mg
Alemtuzumab 24mg
Fingolimod 0.5mg
Fingolimod 1.25mg
Fingolimod 5mg
Glatiramer Acetate 20mg (Copaxone)
IFN beta-1a 22mcg (Rebif)
IFN beta-1a 30mcg (Avonex)
IFN beta-1a 44mcg (Rebif)
IFN beta-1b 250 mcg (8mlu) (Betaferon)
Natalizumab 300mg (Tysabri)
ACTH
Acyclovir
AG284
anti-CD4-cM-T412
Anti-lymphocyte Globulin + Prednisolone + Azathioprine
Azathioprine
Azathioprine + Methylprednisolone
Bee venom
bovine myelin
Chaperonline 10mg
Chaperonline 5mg
Cladribine 0.7 mg/kg
Cladribine 3.5mg p.o.
Cladribine 5.25 mg p.o.
Fampridine 10mg
Fampridine 15mg
Fampridine 20mg
fluoxetine

5. Choose a MS type (optional)

Network of multiple treatments in Multiple Sclerosis
NET - MS

User Login (NET-MS)
Change Password
Forgot Password

Outcome: Relapse free patients

Treatment of interest: Fingolimod 5mg

Comparator treatment: ALL

MS type: **ALL** (selected)
CPMS
MIXED
PPMS
PPMS and SPMS
PRMS and SPMS
RRMS
RRMS and CIS
RRMS and PPMS and SPMS
RRMS and PRMS
RRMS and PRMS and SPMS
RRMS and SPMS
SPMS

SPC of treatment of interest

SPC of comparator treatment

Published RCTs for treatment of interest

Type of analysis:
Individual RCTs direct analysis
Direct pooled analysis
Indirect analysis

6. Choose a year of interest (optional)

Network of multiple treatments in Multiple Sclerosis
NET - MS

User Login (NET-MS)
Change Password
Forgot Password

Outcome: Relapse free patients

Treatment of interest: Fingolimod 5mg

Comparator treatment: ALL

MS type: ALL

Grouping: ALL

Type of analysis: ALL

From year: 1987 (selected)
1982
1983
1984
1985
1986
1987
1988
1989
1990
1991
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011

SPC of treatment of interest

SPC of comparator treatment

Published RCTs for treatment of interest

Type of analysis:
Individual RCTs direct analysis
Direct pooled analysis
Indirect analysis

7. SPCs for treatment of interest and comparator treatment are available (optional). For details go on page 10

The screenshot shows the NET-MS web application interface. The browser address bar displays the URL: <http://netms.med.uth.gr/default.aspx?id=27888EC7-EC41-4F05-8D04-06D1383DAD67>. The page title is "Network of multiple treatments in Multiple Sclerosis NET - MS". On the left, there is a sidebar with links: "User Login (NET-MS)", "Change Password", and "Forgot Password". The main content area contains a form with the following fields:

- Outcome: Relapse free patients
- Treatment of interest: Fingolimod 5mg
- Comparator treatment: ALL
- MS type: ALL
- Grouping MS: ALL
- Type of analysis: ALL
- From year: ALL
- to year: ALL

Below the form, there are three buttons: "SPC of treatment of interest", "SPC of comparator treatment", and "Published RCTs for treatment of interest". The "SPC of treatment of interest" and "SPC of comparator treatment" buttons are highlighted with red arrows. Below these buttons, there is a section titled "Type of analysis" with three options: "Individual RCTs direct analysis", "Direct pooled analysis", and "Indirect analysis".

8. Published RCTs for treatment of interest are available (optional). For details go on page 12

The screenshot shows the NET-MS web application interface. The browser address bar displays the URL: <http://netms.med.uth.gr/default.aspx?id=27888EC7-EC41-4F05-8D04-06D1383DAD67>. The page title is "Network of multiple treatments in Multiple Sclerosis NET - MS". On the left, there is a sidebar with links: "User Login (NET-MS)", "Change Password", and "Forgot Password". The main content area contains a form with the following fields:

- Outcome: Relapse free patients
- Treatment of interest: Fingolimod 5mg
- Comparator treatment: ALL
- MS type: ALL
- Grouping MS: ALL
- Type of analysis: ALL
- From year: ALL
- to year: ALL

Below the form, there are three buttons: "SPC of treatment of interest", "SPC of comparator treatment", and "Published RCTs for treatment of interest". The "Published RCTs for treatment of interest" button is highlighted with a red arrow. Below these buttons, there is a section titled "Type of analysis" with three options: "Individual RCTs direct analysis", "Direct pooled analysis", and "Indirect analysis".

9. Choose a type of analysis. (Please click only once on the button of your choice)

Outcome: Relapse free patients

Treatment of interest: Fingolimod 5mg

Comparator treatment: ALL

MS type: ALL

Grouping MS: ALL

Type of analysis: ALL

From year: ALL to year: ALL

SPC of treatment of interest

SPC of comparator treatment

Published RCTs for treatment of interest

Type of analysis

- Individual RCTs direct analysis
- Direct pooled analysis
- Indirect analysis
- Combined analysis

10. Wait until data appears to the screen. Please click only once (on your first choice and wait for the results). Then you may continue with your second, third and fourth choice)

Fingolimod 5mg vs Placebo

Direct Analysis				
	OR	95% LL	95% UL	Inference
Fingolimod 5mg vs Placebo	3.38798	1.60836	7.13672	Fingolimod 5mg shows significantly better outcome than Placebo ($P < 0.05$)

Page Updated: 28/08/2013
NET-MS DB Updated: 19/08/2012

Results are
presented
as above

(3) More

3a. Type of analysis options

Individual RCTs direct analysis

All RCTs that have been published comparing direct the selected treatments are displayed to year of publication.

Direct pooled analysis

All RCTs having been published comparing direct the selected treatments are used and meta-analysis results are provided. A direct meta-analysis is conducted and the random effects (RE) OR is calculated, according to DerSimonian and Laird. The RE model is used instead of the fixed effects model because it is more conservative. Heterogeneity between studies is tested using the Q-statistic, and it is quantified with the I² metric, which is independent of the number of studies included in the meta-analysis. Number of studies used is also provided.

Indirect analysis

In the indirect comparison of treatments selected (A and B), in which each treatment has been compared directly with a common treatment (C), the OR of A versus B was calculated as follows: $\ln(\text{OR}_{\text{AvsB}}) - \ln(\text{OR}_{\text{AvsC}}) - \ln(\text{OR}_{\text{BvsC}})$, and the respective 95% (CI) is estimated assuming asymptotic normality and lack of covariance, as described by Glenny et al and Song et al.

Combined analysis

In combining the studies for direct or indirect comparisons, the inverse variance method was used, as described previously.

3b. What else can be found?

3b-1. SPC of treatment of interest and comparator treatment

The user can retrieve the SPC of the selected treatments. SPC data are retrieved from the following web address: medicines.org.uk.

Network of multiple treatments in Multiple Sclerosis
NET-MS

User Login (NET-MS)
Change Password
Forgot Password

Outcome: Relapse free patients
Treatment of interest: IFN beta-1b 250 mcg (8miu) (Betaferon)
Comparator treatment: Placebo
MS type: ALL
Grouping MS: ALL
Type of analysis: ALL
From year: ALL to year: ALL

SPC of treatment of interest
SPC of comparator treatment
Published RCTs for treatment of interest

Type of analysis
Individual RCTs direct analysis
Direct pooled analysis
Indirect analysis
Combined analysis

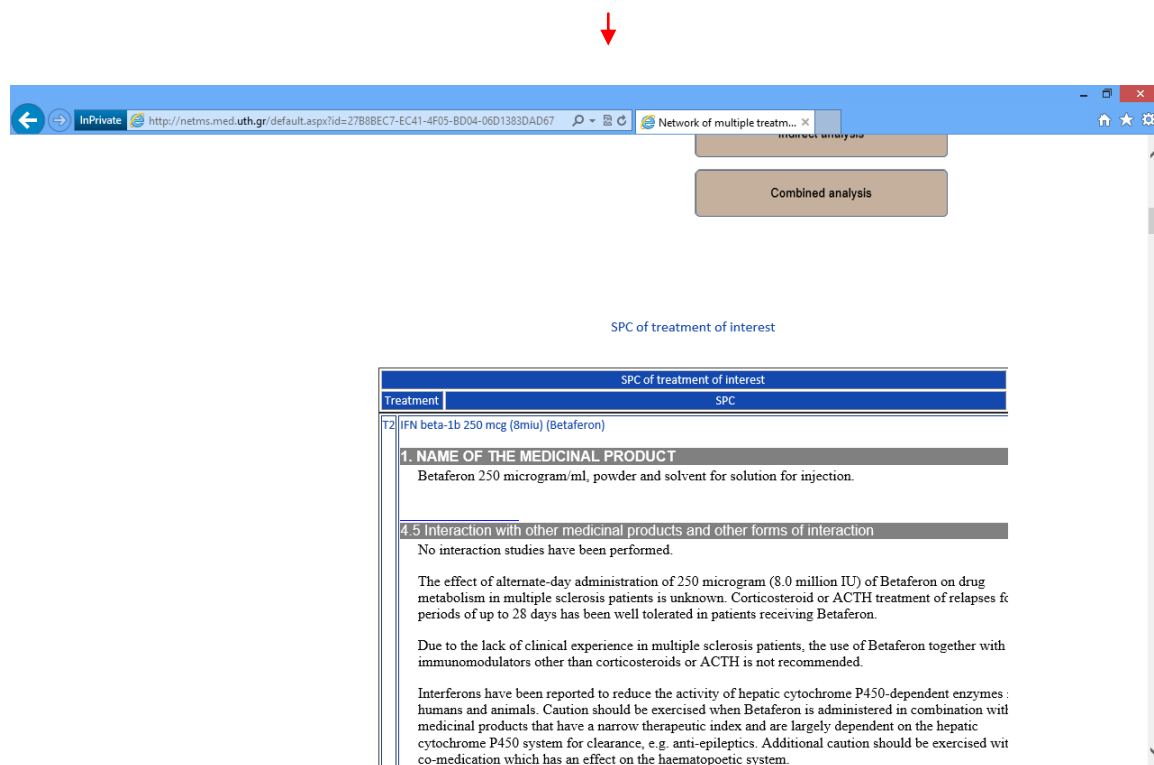
Published RCTs for treatment of interest

Type of analysis
Individual RCTs direct analysis
Direct pooled analysis
Indirect analysis
Combined analysis

SPC of treatment of interest

SPC of treatment of interest	
Treatment	SPC
T2	IFN beta-1b 250 mcg (8miu) (Betaferon)
Show SPC Hide SPC	

Page Updated: 28/08/2013
NET-MS DB Updated: 19/08/2012



The screenshot shows a web browser window with the URL <http://netms.med.uth.gr/default.aspx?id=27B88EC7-EC41-4F05-BD04-06D1383DAD67>. The page displays a 'Network of multiple treatm...' and a 'Combined analysis' button. Below this, the 'SPC of treatment of interest' is shown for 'IFN beta-1b 250 mcg (8miu) (Betaferon)'. The SPC table has two columns: 'Treatment' and 'SPC'. The 'Treatment' column lists 'IFN beta-1b 250 mcg (8miu) (Betaferon)'. The 'SPC' column contains the following information:

Treatment	SPC
IFN beta-1b 250 mcg (8miu) (Betaferon)	<p>1. NAME OF THE MEDICINAL PRODUCT Betaferon 250 microgram/ml, powder and solvent for solution for injection.</p> <p>4.5 Interaction with other medicinal products and other forms of interaction No interaction studies have been performed.</p> <p>The effect of alternate-day administration of 250 microgram (8.0 million IU) of Betaferon on drug metabolism in multiple sclerosis patients is unknown. Corticosteroid or ACTH treatment of relapses for periods of up to 28 days has been well tolerated in patients receiving Betaferon.</p> <p>Due to the lack of clinical experience in multiple sclerosis patients, the use of Betaferon together with immunomodulators other than corticosteroids or ACTH is not recommended.</p> <p>Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when Betaferon is administered in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. anti-epileptics. Additional caution should be exercised with co-medication which has an effect on the haematopoietic system.</p>

The electronic Medicines Compendium (eMC) contains up to date, easily accessible information about medicines licensed for use in the UK. The eMC has more than 7,000 documents, all of which have been checked and approved by either the UK or European government agencies which license medicines. These agencies are the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA). All the information on the eMC website comes directly from pharmaceutical companies. eMC is being updated in 30 days' time after a new drug is launched or a change has been approved. Our site updates SPC data every 3 months.

3b-2. Published RCTs of treatment of interest

By clicking on “Published RCTs for treatment of interest” all published RCTs for the selected treatment of interest are appearing on the screen according to the year of publication.

The screenshot shows the NET-MS web application interface. The browser address bar displays the URL: <http://netms.med.uth.gr/default.aspx?id=27B88EC7-EC41-4F05-BD04-06D1383DAD67>. The page title is "Network of multiple treatments in Multiple Sclerosis NET-MS".

On the left, there is a sidebar with links: "User Login (NET-MS)", "Change Password", and "Forgot Password".

The main content area contains a search filter section with the following options:

- Outcome: Relapse free patients
- Treatment of interest: IFN beta-1b 250 mcg (8miu) (Betaferon)
- Comparator treatment: Placebo
- MS type: ALL
- Grouping MS: ALL
- Type of analysis: ALL
- From year: ALL to year: ALL

Below the filters, there are three buttons: "SPC of treatment of interest", "SPC of comparator treatment", and "Published RCTs for treatment of interest". A red arrow points to the "Published RCTs for treatment of interest" button.

Below these buttons, there is a "Type of analysis" section with three options: "Individual RCTs direct analysis", "Direct pooled analysis", and "Combined analysis". A red arrow points to the "Combined analysis" button.

The "Combined analysis" button is selected, and the page displays a table with the following data:

Period	
From Year	To Year
1900	9999

Below the table, there is a section titled "Published RCTs" which displays a list of RCTs. The first RCT is highlighted with a red arrow pointing to the "Show full RCT" button.

Published RCTs	
Author: Cadavid Year: 2009 Journal: Neurology Study name: BECOME MStype: RRMS and CIS Regimen: IFN beta-1b 250 mcg (8miu) (Betaferon)	Efficacy of treatment of MS with IFN -1b or glatiramer acetate by monthly brain MRI in the BECOME study Show full RCT Hide RCT
Author: O'Connor Year: 2009 Journal: LancetNeurol Study name: BEYOND MStype: RRMS Regimen: IFN beta-1b 250 mcg (8miu) (Betaferon)	250 µg or 500 µg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study Show full RCT Hide RCT
Author: Durelli Year: 2008 Journal: Jneurol Study name: OPTIMS MStype: RRMS Regimen: IFN beta-1b 250 mcg (8miu) (Betaferon)	The OPTimization of Interferon for MS Study: 375 µg interferon beta-1b in suboptimal responders Show full RCT Hide RCT
Author: Etamadifar	Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting

A red arrow points to the "Show full RCT" button for the first RCT.

The abstract of each RCT appearing on the screen can be easily retrieved by clicking “Show full RCT”.

Combined analysis

Period	
From Year	To Year
1900	9999

Published RCTs

Published RCTs	
Author: Cadavid Year: 2009 Journal: Neurology Study name: BECOME MSType: RRMS and CIS Regimen: IFN beta-1b 250 mcg (8miu) (Betaferon)	Efficacy of treatment of MS with IFN -1b or glatiramer acetate by monthly brain MRI in the BECOME study Background: There are no published MRI studies comparing interferon beta 1b (IFN -1b) and glatiramer acetate (GA) for treatment of relapsing multiple sclerosis (MS). Objective: To compare the efficacy of IFN -1b and GA for uppression of MS disease activity as evidenced on frequent brain MRI. Methods: A total of 75 patients with relapsing-remitting MS or clinically isolated syndromes were randomized to standard doses of IFN -1b or GA and followed by monthly brain MRI for up to 2 years with a protocol optimized to detect enhancement. The primary outcome was the number of combined active lesions (CAL) per patient per scan during the first year, which included all enhancing lesions and nonenhancing new T2/fluid-attenuated inversion recovery (FLAIR) lesions. Secondary outcomes were the number of new lesions and clinical exacerbations over 2 years. Results: Baseline characteristics were similar between the groups. The primary outcome showed similar median (75th percentile) CAL per patient per scan for months 1–12, 0.63 (2.76) for IFN -1b, and 0.58 (2.45) for GA (p 0.58). There were no differences in new lesion or clinical relapses for 2 years. Only 4.4% of CAL on monthly MRI scans were nonenhancing new T2/FLAIR lesions. Conclusion: Patients with relapsing multiple sclerosis randomized to interferon beta 1b or glatiramer acetate showed similar MRI and clinical activity Show full RCT Hide RCT

Author: O'Connor
250 vs 500 vs Interferon beta-1b versus 70 mg glatiramer acetate in relapsing-

3c. Which metrics are used and what do they mean?

The results of comparisons are presented as OR (odds Ratio) and 95 % CI (confidence interval). If $OR > 1$ then the treatment of interest shows significantly better outcome; however, if the $OR < 1$ then the treatment of interest shows significantly worse outcome than the comparator treatment. If the 95% CI of the OR contains the value of 1, then, the treatment of interest does not show significantly better or worse outcome than the treatment of interest. However, if the 95% CI of the OR does not contain the value of 1, then, the OR is significant, and the treatment of interest does show significant outcome as many times as the OR value.

Let choose as outcome the “Patients without disease progression”, treatment of interest the “Glatiramer Acetate 20 mg (Copaxone)” and comparator treatment the “Placebo”. Also, let select the “Indirect analysis” option. The results of the analysis are $OR = 2.98668$ and 95% CI (1.76104- 5.06535). This finding imply that Copaxone is significantly 3-fold (3 times) better response (outcome) than placebo ($OR = 2.99$) and this outcome is significant since the 95%CI does not contain the value of 1. An OR of 2.99, indicates in patients receiving Copaxone, there is more chance (3 times) of being without disease progression, than in patients receiving placebo.

In the field “**inference**” at the interface, the inference of the analysis along with the results are also shown, i.e. the OR and the respective 95%. CI.

Glatiramer Acetate 20mg (Copaxone) vs Placebo

Indirect analysis				
	OR	95% LL	95% UL	Inference
Glatiramer Acetate 20mg (Copaxone) vs Placebo	2.98668	1.76104	5.06535	Glatiramer Acetate 20mg (Copaxone) shows significantly better outcome than Placebo ($P < 0.05$)
Number of studies: 21				