“Natalizumab versus Interferon β-1b to prevent CDMS in patients with CIS and poor prognostic factors”

Research protocol

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1. ABSTRACT

About 85% of multiple sclerosis (MS) cases start as clinically isolated syndrome (CIS). When patients present with a CIS, clinicians face with many questions, most of them related with prognosis and treatment. Thereby, patients with CIS have been focus of research. Several studies have demonstrated a relationship between positive IgM lipid-specific oligoclonal band pattern in CSF and higher lesion load on MRI brain scan, higher number of relapses and greater disability, even at the first stages of the disease. On the other hand, no studies have used this previous evidence to treat with more aggressive disease modifying therapy in initial stages of disease course to prevent the earlier axonal damage.

The aim of this study is to assess the most effective approved treatment for MS and current therapy for CIS patients presenting high risk to develop CDMS and with bio-markers of poor prognosis. Among this group of patients any disease activity will eventually lead to disability. Therefore, the earlier the treatment is initiated, the more effective to prevent disability will be. It is considered that “time lost is brain lost” and since once damage is established, there is no therapy to be regained later on.

In this phase III clinical trial, 172 patients will be randomized 1:1 to receive Interferon β-1b or natalizumab over 96 weeks. Time to develop clinical definitive multiple sclerosis (CDMS) will be included as primary endpoint. Other secondary endpoints will include clinical data, magnetic resonance imaging (MRI) measurements and quality of life tests.

2. INTRODUCTION

2.1 Epidemiology

Multiple sclerosis (MS) is the most common chronic demyelinating disease of the central nervous system (CNS) and the second cause of disability in young adults after brain traumatic injuries. With unknown aetiology, there are several evidences to corroborate that it is an autoimmune disease [1, 2]. The prevalence of MS in Spain is between 40 and 125 cases for 100.000 inhabitants depending on the studies and there is a female preponderance [2]. MS is between twice and three times more common in women than in men, and the global incidence is increasing [2, 3].

2.2 Risk factors

Currently, the strongest genetic association for MS is the human leukocyte antigen (HLA) gene locus on chromosome 6, specifically certain HLA types as HLA DR15 and DQ6. These genes are involved in antigen recognition by T-cells and may therefore determine whether or not abnormal responses are made towards myelin proteins [2, 4, 5].

Large-scale epidemiological and migration studies indicate that certain environmental risk factors are associated with the development of MS. These factors are thought to affect the immune system and include: prior infection with Epstein-Barr virus, smoking and vitamin D deficiency related to sunlight exposure or diet [4,5].

2.3 Pathogenesis

The pathogenesis of MS comprises three different characteristics: inflammation, demyelination and axonal damage.

Multiple sclerosis as an autoimmune disease: In genetically susceptible individuals, through a process of immune dysregulation and probably mistaken antigen identity, CD4 T-cells become primed in the peripheral blood and cross the blood-brain barrier, where they recognize components of the myelin sheath. The subsequent release of cytokines activates macrophages and B-cells [2,4,6,7].

Multiple sclerosis as a demyelinating disease: Demyelination is a central feature of MS lesion pathology. There are different patterns of demyelination: T-cell and macrophage mediated, antibody mediated involving complement activation, oligodendrogliopathy, oligodendrocyte apoptosis and oligodendrocyte degeneration[2,6].

Multiple sclerosis as a neurodegenerative disease: Parallel to inflammatory phase associated with demyelization, axonal loss responsible for irreversible disability occurs already early in the disease course [2, 3, 4].

2.4 Diagnosis

The diagnosis of MS is mainly clinical and it is based on the confirmation dissemination of lesions in time and space after the exclusion of other aetiologies. It requires the integration of clinical history, neurological examination, MRI scanning and the profile of cerebrospinal

fluid [8].

The McDonald criteria [9] were designed to simplify diagnosis and are the most used today both clinical practice and research. MRI is the most important diagnostic tool for demonstrating dissemination in time and space.

2.5 Clinical course

85% of MS patients present a relapsing-remitting course [2, 4]. It is characterized by relapses with focal neurological deficits than could improve totally or partially leaving sequels. With time, recovery from each episode is incomplete and persistent symptoms accumulate. Eventually, around 65% of patients enter to the secondary progressive phase of the disease [3]. In 15% of patients the clinical course is progressive from onset [2, 3].

Usually, (80-85%) the disease presents with a first attack. This initial episode of focal demyelination is known as a clinically isolated syndrome (CIS) [2,3]. However, not all CIS patients develop MS and its disability progression can be highly variable. In the last years, several studies have tried to find prognostic factors that might predict future disease course. These main prognostic factors are:

- Number of lesions in the first MRI [10-12].
- Presence of IgG oliclonals bands in the CSF. They are present in nearly 95% of MS patients, for this reason it is a good tool to predict conversion to clinically definitive multiple sclerosis (CDMS) but not to predict the severity of the clinical course [14].
- Intrathecal IgM synthesis are present in nearly 40% of the CSF of MS patients and it is related with several factors of poor prognosis [13-19]:
    - The time to a second relapse after a CIS.
    - The time to reach disability (EDSS of 4.0).
    - The time to develop a secondary progressive phase of the disease.
    - The increases in early brain atrophy.
    - The increases in T2 lesion load.

The most recent works have demonstrated that IgM against lipids are the specific IgMs which are related with an aggressive course and the involvement in plaque formation [13, 14, 16, 17, 18,19].

2.6 Treatment

2.6.1 First-line of treatment

The first line of treatment includes disease modifying drugs authorized for use after establishing the diagnosis. It is allowed to start treatment with any of them and they are also interchangeable whether it is considered [8, 21].

Beta Interferons: Interferons are a family of pleiotropic cytokines produced by cells in response to viral infections. These cytokines exhibit antiviral, immunomodulatory and antitumor properties by regulating expression of hundreds of genes involved in biological processes such as cell cycle progression, cell proliferation and apoptosis [23]. The exact mechanism of action of IFN-β in MS is complex and is not clearly understood, it increases production of anti-inflammatory agents such as IL-10 and decreases production of pro-inflammatory cytokines such as IL-17. It also inhibits immune cell trafficking across the blood–brain barrier and stimulates the production of trophic factors such as nerve growth factors [22-24]. There are differents forms of presentation (table I).

Drug	Brand	Recomended dose	Dosing frequency	Route
Interferon beta-1a	Avonex	30 mcg	Once weekly	IM
Interferon beta-1a	Rebif	22 or 44 mcg	Three times weekly	SQ
Interferon beta-1b	Betaferon	0,25 mg	Every other day	SQ
Interferon beta-1b	Extavia	0,25 mg	Every other day	SQ

Taula 1: Interferons FDA approved. IM= intramuscular, SQ= subcutaneous

Glatiramer Acetate: Glatiramer acetate (GA) is a polypeptide made up of four amino acids (L-glutamic acid, L-lysine, L-alanine, and L-tyrosine). Its mechanisms of action are not completely understood, but several studies indicate that GA causes an immune deviation from a Th1 to a Th2 phenotype, induces antigen-specific T suppressor cells that react with autoantigens in the CNS, and inhibits antigen presentation [24]. The form of presentation is route subcutaneous, once daily with 20 mg as a recommended dose [22].

2.6.2 Second-line of treatment

In MS, a drug is considered as second-line when its use is subject to failure or intolerance of previous first-line treatments [8, 21].

Fingolimod: Fingolimod is a sphingosine-1-phosphate receptor modulator that is metabolized by sphingosine kinase to the active metabolite fingolimod phosphate, which

blocks the migration of lymphocytes from lymph nodes and reduces the number of lymphocytes in peripheral blood. The mechanism that is the basis of the therapeutic effect of fingolimod in MS is unknown, but it might involve the reduction of lymphocyte migration into the CNS [21-23].

Natalizumab: Natalizumab is a recombinant humanised monoclonal antibody that binds to the α4 subunit of 41 integrin (VLA-4) on the surface of lymphocytes. This action blocks the binding of the subunit to its receptor (VCAM-1), which is present in the endothelium. This action prevents lymphocytes from crossing blood brain barriers and entering in the central nervous system, reducing the pathological process of MS [21-23].

In a randomized, placebo-controled trial of natalizumab for relapsing multiple sclerosis [25] were enrolled 942 patients, 627 were assigned to receive natalizumab every 4 weeks and 315 to receive placebo by intravenous . The study demonstrated the following aspects of efficacy:

- Reduction the rate of clinical relapses at one year by 68% ($p<0.001$).
- Reduction the risk of sustained progression of disability by 42% (hazard ratio 0.58 CI (0.43 to 0.77).
- Reduction in the accumulation of new or enlarging hyperintense lesions by 83% ($p<0.001$).
- Reduction in gadolinium enhancing lesions by 92% ($p<0.001$).

2.6.3 Natalizumab management

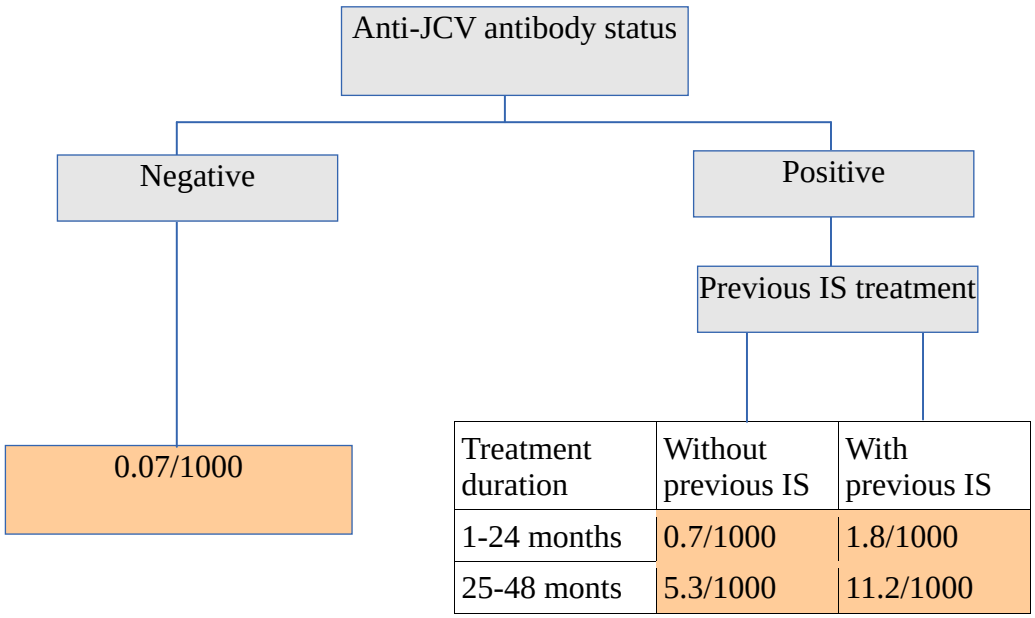
Natalizumab is the most effective therapy at reducing relapses and delaying disease progression in MS [25]. On the other hand, this treatment has also been associated with a risk of progressive multifocal leukoenchephalopathy (PML). For this reason, its use needs to be considered carefully and established a benefit-risk balance [32].

On a practical level, currently there are 3 variables to stratify risk of PML (figure 1):

- Presence/absence of anti-JC virus antibodies.
- Presence/absence of previous immunosuppressive (IS) therapy.
- Treatment duration in months: more than o less than 24 months.

The treatment with natalizumab in this study will be over 2 years in order to have a

minimum risk to develop LMP. Also, a current study [30] has demonstrated in two independent cross-sectional and two longitudinal sets of patients that natalizumab decrease IgM and IgG levels within the first two years of therapy.



Treatment duration	Without previous IS	With previous IS
1-24 months	0.7/1000	1.8/1000
25-48 monts	5.3/1000	11.2/1000

Figure 1. Risk to develop LMP

2.7 Current therapies for CIS

CIS stage represents the first opportunity for treatment in patients with high risk of conversion to CDMS. In addition, the presence of early and irreversible axonal damage in CNS of MS patients apparently reduces the benefit of treatment afterwards. Several studies have corroborated treatment with disease-modifying therapies should begin early in the disease course [26, 27].

Three large clinical trials have shown that IFNβ treatments are effectiveness in CIS patients:

- Controlled High-Risk Avonex MS prevention Study (CHAMPS).
- Early treatment of MS (ETOMS).
- Betaferon in newly emerging MS for initial treatment (BENEFIT).

The CHAMPS study [28] enrolled 383 CIS randomized to two groups: 193 once-weekly IFNβ-1a versus 190 placebo injections. CDMS was defined by second attack or increase of at least 1.5 points on the EDSS. At 3 years, CDMS was lower in the IFNβ-1a group than in placebo (rate radio (rr) for the cumulative probability of CDMS = 0.56; p= 0.002).

The ETOMS study [29] enrolled 309 CIS randomized to: 154 once-weekly injection of IFNβ-1a versus 155 placebo injections. The results was higher proportion of patients in placebo group than in IFNβ-1a group converted from CIS to CDMS over 2 years (rr for the cumulative probability of CDMS = 0.65; p= 0.047).

In the BENEFIT [30] study were enrolled 468 patients: 292 IFNβ-1b versus 176 placebo. Over 2 years accumulative probability for CDMS was higher in placebo group (rr for the cumulative probability of CDMS = 0,5; p= 0,0001).

Moreover, the study PRECISE [31] has shown that AG presents similar effectiveness than IFNβ in the prevention to develop from CIS to CDMS. For this reason, IFNβ and AG have a class A recommendation to prevent new relapses or new lesions on MRI in cases with high risk of conversion to CDMS (figure2). Health authorities have approved the indication of these drugs for the CIS treatment at the same dose and frequency than in RRMS form [21].

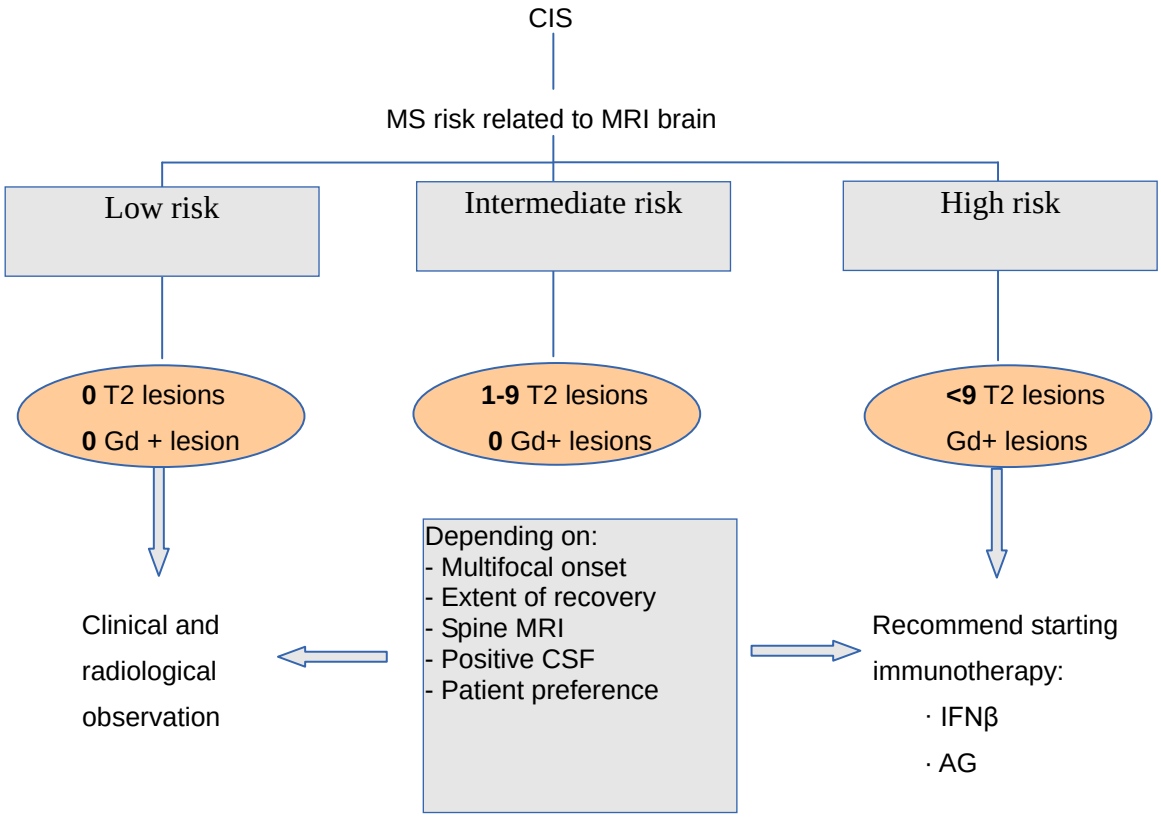


Figure 2. MRI risk to develop CDMS

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4. HYPOTHESIS

Early natalizumab treatment in subjects with CIS and poor prognostiic factors will reduce the development of CDMS compared to interferon β-1b.

Early natalizumab treatment in subjects with CIS and poor prognostic factors will reduce the disability progression and the frequency of relapses after CDMS compared to interferon β-1b.

Early natalizumab treatment in subjects with CIS and poor prognostic factor will reduce the lesion load and brain atrophy compared to interferon β-1b.

Early natalizumab treatment will improve the quality of life in patients with CIS and poor prognostic factors compared to interferon β-1b.

5. OBJECTIVES

5.1 Primary objective

1. To assess natalizumab compared to interferon β-1b in reduction of CDMS in subjects with CIS and factors of poor prognosis over 96 weeks.

5.2 Secondary objectives

Clinical objectives: to assess the effect of natalizumab compared to Interferon β-1b on:

2. Disability progression in subjects with CIS and poor prognosis factors over 96 weeks.
3. Frequency of relapses in subjects with CIS and poor prognostic factors over 96 weeks.

MRI objectives: to assess the effect of natalizumab compared to interferon β-1b on:

4. Total volume of T2 hyperintense lesions over 96 weeks.
5. Number of new gadolinium enhancing lesions over 96 weeks.
6. Number of new T1 hypointense lesions over 96 weeks.
7. Brain atrophy developed over 96 weeks.

Quality of life objectives: to assess the effect of Natalizumab compared to Interferon β-1b on:

8. Fatigue.
9. Health-related quality of life.

6. METHODS

6.1 Study design

This is an interventional and multi-center study. The allocation will be randomized, the intervention model will be parallel assignment in 2 groups and the masking will be double blind. Study participants and observers will not know treatment assignments.

The treatment duration is 96 weeks for the last patient recruited. The treatment period will have a fixed time of 96 weeks for all patients. For those patients who complete the treatment period, a follow up extension will have a minimum duration of 6 months in order to observe and detect potential side effects.

6.2 Inclusion and exclusion criteria

Inclusion criteria

1. Age ranging from 18 to 55 years.
2. Understanding and accepting the purpose and the risks of this study signing the informed consent.
3. Must have a confirmed diagnosis of CIS according to both clinical and cranial MRI.
4. Must have all the following risk factors to develop an aggressive CDMS:
   - 1-9 T2 hyperintense lesions and gadolinium enhancing lesions or more than 9. T2 hyperintense lesions.
   - Positive IgG and IgM-LS oligoclonal bands in CSF.
5. Must have at most 1 risk factor of the following to develop LMP:
   - Presence of anti-JC virus antibodies.
   - Presence of previous immunosuppressive (IS) therapy.
   - Treatment duration in months: more than 24 months.
6. Baseline assessment, clinical, MRI and CSF performed less than 1 month from clinical onset.

Exclusion criteria

1. Diagnosis of MS in any disease course: relapsing-remitting, secondary progressive or primary progressive form.
2. Diagnosis of radiological isolated syndrome (RIS).
3. Diagnosis of CIS but without having all the following risk factors to develop an

aggressive CDMS:

- 1-9 T2 hyperintense lesions and gadolinium enhancing lesions or more than 9 T2 hyperintense lesions.
- Positive IgG and IgM-LS oligoclonal bands in CSF.

4. More than 1 risk factor to develop LMP.
5. Liver function impairment or persisting elevations (confirmed by retest) of serum glutamic pyruvic transaminase (SGPT/ALT), serum glutamic oxaloacetic transaminase (SGOT/AST), or direct bilirubin greater than 3-5 fold the upper limit of normal.
6. Known history of hepatitis B or C.
7. Human immunodeficiency virus (HIV) positive patients.
8. Previous history of major psychiatric or neurological disturbances.
9. Women who are currently pregnant/ breast feeding or they want to be pregnant/ breast feeding over study period.

6.3 Sample size

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a one-sided test, 86 subjects in the active intervention group with 60 conversions and 86 reference subjects with 60 conversions are required, assuming that the conversion rate at 1, 12.5 and 24 moments among the reference subjects will be 0.1, 0.3 and 0.9 while in the active intervention group will be 0.02, 0.13 and 0.84 respectively. It has been anticipated a drop-out rate of 5%.

6.4 Randomization and masking

The patients will be randomized using a 1:1 randomization ratio between two groups:

- Group 1: Nearly 86 patients. Natalizumab 300 mg infusion every 4 weeks plus placebo (sc) every-other day.
- Group 2: Nearly 86 patients. Interferon β-1b 0.25 mg (sc) every-other day plus placebo infusion every 4 weeks.

In order to assure blinding procedures, one neurologist will be the treating and another one will be the examining or blind neurologist.

6.5 Variables for the analysis of goals

6.5.1 Primary endpoint

The primary endpoint in this study is the time to develop CDMS. According to Mc Donald criteria, CDMS is defined as the occurrence of a new neurological event lasting more than 24h and involving a different part of the brain at least 1 month after the end of a previous one.

6.5.2 Clinical endpoints

Disability progression will be assessed using EDSS [Annex I]. Sustained disability progression is defined as:

- At least 1.0 point increase on the EDSS from baseline EDSS ≥ 1.0 that is sustained for 12 weeks.
- At least 1.5 point increase on the EDSS from baseline EDSS = 0 that is sustained for 12 weeks.

The relapses will be assessed using the annualized relapse rate (ARR). The ARR will be calculated as the total number of relapses in the treatment group divided by the number of days in the study, and the ratio multiplied by 365.

A relapse of multiple sclerosis is defined as the occurrence, the recurrence, or the worsening of symptoms of neurologic dysfunction that lasted more than 24 hours and that are stabilized or eventually resolved either partially or completely. Fatigue alone and transient fever-related worsening of symptoms are not considered relapses. Symptoms that occurred within a month after the initial symptoms of relapse are considered to be part of the same episode.

- Each episode of relapse will be confirmed by the treating neurologist, based on the objective assessments by the examining neurologist.
- Subjects will be instructed to contact their investigator immediately should any symptoms suggestive of an MS exacerbation appear.

6.5.3 MRI endpoints

The MS protocol of MRI brain scan include: T1 SE 3mm, DWI, Dual (proton density + T2), GM only, FLAIR and T1+Gd sequences. This protocol will be performed to assess:

- Total volume of T2 hyperintense lesions.
- Number of new gadolinium enhancing lesions.
- Number of new T1 hypointense lesions.
- Brain atrophy.

6.5.4 Quality of life endpoints

Subject reported-fatigue will be assessed using the Modified Fatigue Impact Scale (MFIS) [Annex II]. The MFIS is a validated specific subject-reported outcome measure that was developed to evaluate the impact of fatigue on the lives of people with MS. The instrument can be self-interviewer or telephone-administered and consists of a total score and 3 subscales to assess the impact of fatigue on:

- Cognitive function
- Physical function
- Psychosocial function

The MFIS takes approximately 10 minutes to complete.

Health-related quality of life will be assessed using the Multiple Sclerosis Quality of Life-54 (MSQOL-54) [Annex III]. The MSQOL-54 is a multidimensional health-related quality of life measure that combines both generic and MS-specific items into a single instrument. This 54-item instrument generates 12 subscales along with two summary scores, and two additional single-item measures. The subscales are: physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life, and sexual function. The summary scores are the physical health composite summary and the mental health composite summary. The single item measures are satisfaction with sexual function and change in health.

6.6 Statistical analysis

Quantitative, parametric and continuous variables will be expressed as mean and standard deviation. Quantitative, continuous but non-parametric variables will be expressed as median and interquartile range. Qualitative variables will be described as percentages.

Analysis of primary variable

- Time to develop CDMS will be calculated using log-rank test as a first analysis and

adjusted by Cox proportional regression.

Analysis of secondary variables

- Time to confirmed EDSS progression will be calculated as the same manner of primary variable.
- MRI results, FIS and MSQOL-54 scores will be analysed with non-parametric ANCOVA.

6.7 Study procedures and data collection

The visit schedule is performed with the following items:

- Screening (from week - 4 to week 0).
- Treatment period (from week 0 to week 96).
    - Randomization at baseline.
    - Clinical visits: will be performed every 4 weeks.
    - MRI: will be performed every 6 months.
    - Safety laboratory units: will be performed every 4 weeks between clinical visits until the end of the treatment period.
- Follow up period: will be performed for 6 months after end of treatment.
- Unscheduled visits: will be performed when MS relapse will be suspected.

6.7.1 Screening

The following items will be checked or performed and recorded:

- Review of inclusion and exclusion criteria.
- Clinical laboratories: haematology, coagulation, liver function, electrolytes levels, renal function, urinalysis panel and pregnancy test.
- Informed consent for HIV testing and HIV test.
- Determination of the EDSS score by the examining neurologist and review by the treating neurologist.
- Determination of the number of lesions using MRI brain scan based on MS specific protocol.
- Information on adverse events and informed consent signature.

6.7.2 Randomization:

Prior to randomization, the following items will be checked or performed and recorded:

- Verification of eligibility by review of inclusion and exclusion criteria.
- Physical examination and vital signs.
- Information on adverse events.
- Clinical laboratories: haematology, coagulation, liver function, chemistry panel, renal function, urine analysis and pregnancy test.
- Determination of the EDSS scores.
- Measurement of the MFIS scores.
- Measurement of the MSQOL-54 scores.

After randomization the first dose of study drug endovenous will be administrated and a kit with study drug subcutaneous injections. In order to mask flu-like symptoms, 600 mg of Ibuprofen will be administrated 30 min before each injection as well as 6 hours afterwards.

6.7.3 Treatment period

The following assessments will be performed in the clinic visits:

- Dispense study medication: Intravenous therapy and injections for subcutaneous therapy will be provided every 4 weeks.
- Determination of the EDSS score by the examining neurologist and review by the treating neurologist at weeks: 0, 4, 8, 12, 24, 36, 48, 60, 72, 84 and 96.
- Determination of the MFIS and MSQOL-54 score at weeks: 24, 48, 72, 96.
- MRI brain scan at week: 24, 48, 72 and 96. Determination of volume of T2 hyperintense lesions, number of T1 hypointense lesions, number of gadolinium enhancing lesions and brain atrophy at week: 24, 48 and 96. In all MRI performed will be evaluated the presence/absence of LMP first signs.
- Clinical laboratories: haematology, coagulation, liver function, chemistry panel, renal function and urinalysis panel will be performed every 4 weeks until week 96. Serum antibodies against natalizumab will be performed at week 24, 48, 72, 96.

6.7.4 Unscheduled relapse visit

The following items will be checked or performed and recorded:

- A relapse will be confirmed by the examining neurologist and review by the treating neurologist.
- If the patient had had a confirmed relapse:
    - Time since first dose of treatment.
    - The subject will have to sign the informed consent form for re-consent

to continue with the study.

6.7.5 Follow up period

In order to ensure the safety of all patients, the following items will be performed:

- Clinical laboratories: liver function and haematology at week 108 and 120.
- MRI brain scan at week 120 to evaluate the presence/absence of LMP first signs.

7. LIMITATIONS OF THE STUDY

The major limitation of this study is to achieve the estimated sample size. Mainly, this is due to:

- Relatively low prevalence of CIS presentation with poor prognosis factors.
- The IgM pattern band in CSF is positive in only 40% of patients.
- Very restrictive inclusion criteria.
- Patients will not want to participate for the risk of LMP, even though this is low.

Other limitations are:

- The side effects of the study drugs can impair the blinding process and induce a procedure bias.
- The high cost to perform the study.

8. TREATMENTS

8.1 Natalizumab

300 mg of natalizumab will be infused in 100 mL 0,9% sodium chloride injection over approximately one hour (infusion rate 5 mg/ min). After the infusion is complete, flush with 0,9% sodium chloride injection.

The patients will be observed during the infusion and for one hour after the infusion will be completed. The infusion will be promptly discontinued whether any signs or symptoms consistent with hypersensitivity-type reaction will be detected.

8.1.1 Adverse effects

The most common adverse reactions (incidence ≥ 10%) is headache, fatigue, arthralgia,

urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea and rash.

8.1.2 Warnings and precautions

Progressive multifocal leukoencephalopathy

PML is an opportunistic viral infection of the brain caused by the JC virus that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. The risk to develop LMP in patients who are treated with natalizumab is explained in the section 2.6.2.2.

Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, seizures, speech problems, changes in thinking, memory, and orientation leading to confusion and personality changes. Diagnosis of PML is clinical, brain scan including gadolinium-enhanced MRI and cerebrospinal fluid analysis for JC viral DNA.

It is most important withhold natalizumab dosing immediately at the first sign or symptom suggestive of PML.

Herpes encephalitis and meningitis

Natalizumab increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses. If it occurs, this treatment should be discontinued and appropriate treatment for herpes encephalitis or meningitis will be administered.

Hypersensitivity and antibody formation

Hypersensitivity reactions have occurred in patients receiving natalizumab, including serious systemic reactions at an incidence of <1%. These reactions usually occur within two hours of the start of the infusion. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnoea and chest pain. Generally, these reactions are associated with antibodies to natalizumab. Antibodies may be detected and confirmed with sequential serum antibody tests. The treatment will be discontinued if hypersensitivity reaction or antibody formation is detected.

Laboratory test abnormalities

Natalizumab may induce reduction in circulating lymphocytes, monocytes, eosinophils, basophils and nucleated red blood cells. Changes persist during treatment period but return to baseline levels usually within 16 weeks after the last dose.

Hepatotoxicity

Clinically significant liver injury, including acute liver failure requiring transplant, has been reported, although very few cases, in patients treated with natalizumab. The treatment will be discontinued in patients with evidence of significant liver injury.

8.2 Interferon β-1b

0.25 mg will be injected by route subcutaneous every-other-day. The initial dose will be 0.0625 mg every-other-day and will increase over 6 weeks period to 0.25 mg (table 3).

	Extavia dose	Volume
Week 1-2	0.0625 mg	0.25 mL
Week 3-4	0.125 mg	0.50 mL
Week 5-6	0.1875 mg	0.75 mL
Week 7 and thereafter	0.25 mg	1 mL

Table 3. Schedule for dose titration

8.2.1 Adverse effects

The most common adverse reactions (incidence ≥ 5%) are: injection site reaction, lymphopenia, flu-like symptoms, myalgia, leukopenia, neutropenia, increased liver enzymes, headache, hypertonia, pain, rash, insomnia, abdominal pain, and asthenia.

8.2.2 Warnings and precautions

Anaphylaxis

Anaphylaxis has been reported as a rare complication of interferon β-1b use but if it occurs, the treatment will be discontinued.

Depression and suicide

Depression and suicide have been reported to occur with increased frequency in patients receiving interferon beta products, including interferon β-1b. If a patient develops

depression, discontinuation of the therapy should be considered.

Injection site necrosis

Typically, injection site necrosis occurs within the first 4 months of therapy. The necrotic lesions are usually 3 cm and rarely larger areas are affected. The treatment will be discontinued if multiple lesions occur.

Flu-like symptom complex

It is one of the most common side effects among patients using interferon β-1b but the incidence decreases over treatment period. Normally the median duration is 7 days. Analgesics and antipyretics on treatment days may help flu-like symptoms.

8.3 Acute therapy for relapses during the study

Relapses may be treated with systemic corticosteroids if clinically necessary and as per investigator judgment. The preferred standardized treatment is methylprednisolone sodium succinate 1 g, intravenously daily for 3 days.

9. ETHICAL ASPECTS

This clinical trial will be conducted according to the ethical principles which have their origin in:

- Universal Declaration of Human Rights (1948).
- The Nuremberg Code (1949).
- The Declaration of Helsinki (1964) and its last update in Edinburgh, Scottish (2000).
- Ethical and methodological aspects of Good Clinical Practice in the European Union.

This study will not be started before the favourable opinion of Ethics Committee in each hospital.

All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand. Prior to a patient’s participation in the Clinical Trial, the written Informed Consent Form should be signed, name filled in and

personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

This Clinical Trial will be conducted in compliance with all international laws and regulations, and national laws and regulations of the country or countries in which the Clinical Trial will be performed, as well as any applicable guidelines.

An insurance will be taken out by the sponsor in order to cover damages or serious side effects related to study drugs. This insurance policy will be in accordance with local laws and requirements in each country. An insurance certificate will be provided to the Ethics committees or Health Authorities in countries requiring this document.

10. BUDGET

The budget will be calculated for each study participant and adjusted for estimated total sample size. The study drugs will be provided by the sponsor.

Description	Amount	Cost	Total
MRI	6	200,00 €	1.200,00 €
Clinical visits	12	50,00 €	600,00 €
Nursery visits	24	20,00 €	480,00 €
Safety laboratory analysis	24	30,00 €	720,00 €
IgM band determination	1	50,00 €	50,00 €
		TOTAL	**3050,00 €**

Description	Cost
172 participants	524.600,00 €
Statical analysis	200,00 €
20% Research centre overhead	104.960,00 €
TOTAL STUDY COST	**629.760,00 €**

ANNEX

I. EDSS

II. MFIS

III. MSQOL-54

IV. Informed sheet for patient

V. Informed consent

neurostatus

Standardised Neurological Examination and Assessment of Kurtzke's *Functional Systems*[1] and *Expanded Disability Status Scale*[1]

SOURCE DOCUMENT

SUBJECT NO/SUBJECT INITIALS

COUNTRY/CENTRE NO

NAME OF EDSS RATER

DATE OF EXAMINATION

[1] slightly modified from J. F. Kurtzke, Neurology 1983;33,1444-52

GENERAL GUIDELINES

To ensure unbiased EDSS assessment, the EDSS rater should not inquire about the patients' condition except as necessary to perform the EDSS assessment.

Patients must be observed to walk the required distance.

NEUROSTATUS (NS)

In the Neurostatus «signs only» is noted when the examination reveals signs of which the patient is unaware.

FUNCTIONAL SYSTEMS (FS)

A score of 1 in the Functional Systems implies that the patient is not aware of the deficit and that the deficit or sign does not interfere with normal daily activities (with the exceptions of optic, vegetative and cerebral functions).

EXPANDED DISABILITY STATUS SCALE (EDSS)

EDSS should not be lower than the highest score of the FS. Symptoms which are not MS-related will not be taken into consideration for assessments, but should be noted.

In the definitions of EDSS grades 6.0 and 6.5 both a description of assistance required and of the walking range are included. In general, the distinction of bilateral versus unilateral assistance required to walk overrules the walking range.
However, the following exceptions are suggested,
If a patient is able to walk considerably longer than 100 m with two sticks, crutches or braces he is in grade 6.0.
If a patient is able to walk more than 10 m and less than 100 m with two sticks, crutches or braces he is in grade 6.5.
If a patient needs assistance by another person (as opposed to one stick, crutch or brace) and/or is not able to walk more than 50 m with one stick, crutch or brace he is in grade 6.5.

VISUAL (OPTIC) FUNCTIONS

Definitions

Visual acuity

The visual acuity score is based upon the line on the Snellen chart at 20 feet (5 m) for which the patient makes no more than one error (use best available correction).

Fields

0 = normal
1 = signs only, deficits present only on formal testing
2 = moderate, patient aware of deficit, but incomplete hemianopsia on examination
3 = marked, complete homonymous hemianopsia or equivalent

Scotoma

0 = none
1 = small, detectable only on formal (confrontational) testing
2 = large, spontaneously reported by patient

Disc pallor

0 = not present
1 = present

OPTIC FUNCTIONS	OD	OS
Visual acuity (corrected)		
Visual fields		
Scotoma		
Disc pallor		

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = disc pallor and/or mild scotoma and/or visual acuity of worse eye (corrected) less than 30/30 (1.0) but better than 20/30 (0.67)
	2 = worse eye with large scotoma and/or maximal visual acuity (corrected) of 20/30 to 20/59 (0.67–0.34)
	3 = worse eye with large scotoma or moderate decrease in fields and/or maximal visual acuity (corrected) of 20/60 to 20/99 (0.33–0.2)
	4 = worse eye with marked decrease of fields and/or maximal visual acuity (corrected) of 20/100 to 20/200 (0.1–0.2); grade 3 plus maximal acuity of better eye of 20/60 (0.3) or less
	5 = worse eye with maximal visual acuity (corrected) less than 20/200 (0.1); grade 4 plus maximal acuity of better eye of 20/60 (0.3) or less
	6 = grade 5 plus maximal visual acuity of better eye of 20/60 (0.3) or less

BRAINSTEM FUNCTIONS

Definitions

Assessment of impairment/disability

0 = normal
1 = signs only
2 = mild, clinically detectable numbness, facial weakness, dysarthria or cranial nerve deficits of which patient is aware
3 = moderate, diplopia with incomplete paralysis of any eye movement, impaired discrimination of sharp/dull in 1 or 2 trigeminal branches, trigeminal neuralgia, weakness of eye closure, cannot hear finger rub and/or misses several whispered numbers, obvious dysarthria during ordinary conversation impairing comprehensibility
4 = severe, complete loss of movement of either eye in one direction, impaired discrimination of sharp/dull or complete loss of sensation in the entire distribution of one or both trigeminal nerves, unilateral or bilateral facial palsy with lagophthalmus or difficulty with liquids, sustained difficulty with swallowing, incomprehensible voice

CRANIAL NERVE EXAMINATION	
EOM (extra ocular movements) impaired	
Nystagmus	
Trigeminal damage	
Facial weakness	
Hearing loss	
Dysarthria	
Dysphagia	
Other bulbar signs	

Nystagmus

0 = normal
1 = signs only
2 = mild, patient feels disturbed
3 = moderate, sustained nystagmus on 30° horizontal or vertical gaze, but not in primary position
4 = severe, sustained nystagmus in primary position or coarse persistent nystagmus in any direction interfering with visual acuity, complete internuclear ophthalmoplegia with sustained nystagmus of abducting eye, oscillopsia

	FUNCTIONAL SYSTEM SCORE
	0 = normal
	1 = signs only
	2a = moderate nystagmus
	2b = other mild disability
	3a = severe nystagmus
	3b = marked extraocular weakness
	3c = moderate disability of other cranial nerves
	4a = marked dysarthria
	4b = other marked disability
	5 = inability to swallow or speak

PYRAMIDAL FUNCTIONS

Definitions ***** = optional

REFLEXES

0 = absent, 1 = weak, 2 = normal, 3 = exaggerated, 4 = cloniform, 5 = inexhaustible (indicate difference between R & L by < or >)

Plantar response

0 = flexor, 1 = neutral, 2 = extensor

Cutaneous reflexes

0 = normal, 1 = weak, 2 = absent

***Palmomental reflex**

0 = absent, 1 = present

LIMB STRENGTH

The weakest muscle in each group defines the score for that group. Each movement should be tested, but only pathological findings should be noted using the BMRC grades. Use of functional tests like jumping with one foot, walking on toes or heels are recommended in order to assess grades 3-5 BMRC.

BMRC Rating scale

0 = no activity, 1 = visible contraction without visible joint movement, 2 = visible movements with elimination of gravity, 3 = movements against gravity possible but impaired, 4 = movements against resistance possible but impaired, 5 = normal strength

FUNCTIONAL TESTS

*Position test UE (upper extremities)
Sinking, 0 = none, 1 = mild, 2 = evident

***Position test LE (lower extremities)**

Sinking, 0 = none, 1 = mild, 2 = evident
1 = only separate lifting possible (grades from horizontal position in hip joints...°)
2 = even separate lifting not possible

***Walking on heals/tiptoes**

0 = normal, 1 = impaired, 2 = not possible

***Monopedal hopping**

0 = normal, 1 = 6–10 times, 2 = 1–5 times, 3 = not possible

LIMB SPASTICITY

0 = normal, 1 = mild, barely increased muscular tone after rapid flexion of an extremity, 2 = moderate, 3 = severe, barely surmountable increased spastic tonus after rapid flexion of an extremity, 4 = contracted

Gait spasticity

0 = normal, 1 = barely perceptible, 2 = evident, minor interference with function, 3 = permanent shuffling, major interference with function

REFLEXES	**R**	**><**	**L**
Biceps			
Triceps			
Radial			
Knee			
Ankle			
Plantar response			
Cutaneous reflexes			
*Palmomental reflex			

LIMB STRENGTH				
Shoulder				
Elbow flexors				
Elbow extensors				
Hand/finger flexors				
Hand/finger extensors				
Hip flexion				
Knee flexors				
Knee extensors				
Foot/toe flexors				
Foot/toe extensors				
*Position test UE, pronation				
*Position test UE, sinking				
*Position test LE, sinking				
only lifting of single leg possible		°		°
*Walking on heals				
*Walking on tiptoes				
*Hopping on one foot				

SPASTICITY		
Arm		
Leg		
Gait		

FUNCTIONAL SYSTEM SCORE

	0 = normal
	1 = abnormal signs without disability
	2 = minimal disability, patient complains about fatiguability in motor tasks and/or BMRC grade 4 in one or two muscle groups
	3a = mild to moderate paraparesis or hemiparesis, full range of movement against gravity 3b = severe monoparesis, refers to BMRC grade 2 or less in one muscle group
	4a = marked paraparesis or hemiparesis 4b = moderate tetraparesis (refers to BMRC grade 3) 4c = Monoplegia
	5a = Paraplegia, grade 0 or 1 in all muscle groups of the lower limbs 5b = Hemiplegia 5c = Marked tetraparesis (BMRC grade 2 or less)
	6 = Tetraplegia (grade 0 or 1 in all muscle groups of upper and lower limbs)

CEREBELLAR FUNCTIONS

Definitions
UE = upper extremities
LE = lower extremities
EO = eyes open
EC = eyes closed

Head tremor, rebound
0 = normal
1 = mild abnormality
2 = moderate abnormality
3 = severe abnormality

Truncal ataxia
0 = none
1 = signs only
2 = mild, swaying with EC
3 = moderate, swaying with EO
4 = severe, unable to sit without assistance

Limb ataxia
0 = none
1 = signs only
2 = mild, tremor or clumsy movements seen easily, minor interference with function
3 = moderate, tremor or clumsy movements interfere with function in all spheres
4 = severe, most functions are very difficult

Gait ataxia
0 = none
1 = signs only
2 = mild, abnormal balance only on heel or toe walking, or walking along a line
3 = moderate, abnormal balance on ordinary walking or while seated
4 = severe, unable to walk more than a few steps or requires support by another person or walking aid because of ataxia

Romberg test
0 = normal
1 = mild, mild insecurity with EC
2 = moderate, not stable with EC
3 = severe, not stable with EO

Straight line walking
0 = without problems
1 = impaired
2 = not possible

Note
The presence of severe gait ataxia alone results in a grade of 3 in the cerebellar FS. If weakness interferes with the testing of ataxia, score the patient's actual performance, but also indicate the possible role of weakness by marking the box marked 'X'.

CEREBELLAR EXAMINATION	
Head tremor	
Truncal ataxia, EO	
Truncal ataxia, EC	

	R	**L**
Tremor/dysmetria UE		
Tremor/dysmetria LE		
Rapid alternate movements impaired UE		
Rapid alternate movements impaired LE		
Gait ataxia, EO		
Straight line walking, EO		
Other, e.g. rebound		
Romberg test		

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = abnormal signs without disability
	2 = mild ataxia
	3a = moderate truncal ataxia 3b = moderate limb ataxia
	4 = severe ataxia in all limbs or trunk
	5 = unable to perform coordinated movements due to ataxia
	X = weakness (grade 3 or more on pyramidal) interferes with testing

SENSORY FUNCTIONS

Definitions
UE = upper extremities
LE = lower extremities

***** = optional

Superficial sensation – Touch/pain
0 = normal
1 = mild, patient is aware of impaired light touch or pain, but able to discriminate sharp/dull
2 = moderate, impaired discrimination of sharp/dull
3 = severe, no discrimination of sharp/dull and/or unable to feel light touch
4 = complete loss, anaesthesia

Vibration sense
0 = normal
1 = mild, graded tuning fork 5–7 of 8 (alternatively) detects more than 10 sec. but less than examiner
2 = moderate, graded tuning fork 1–4 of 8 (alternatively) detects more than 2 sec. but less than 11 sec.
3 = marked, complete loss of vibration sense

Position sense / Romberg test
0 = normal
1 = mild, 1–2 incorrect responses on testing, only distal joints affected/slight stagger during Romberg testing
2 = moderate, misses many movements of fingers or toes, proximal joints affected/unable to stand during Romberg testing without assistance
3 = marked, no perception of movement/astasia

***Lhermitte**
0 = negative
1 = positive

***Paraesthesia (tingling)**
0 = none
1 = present

SENSORY EXAMINATION	R	L
Superficial sensation (touch/pain) UE		
Superficial sensation trunk		
Superficial sensation LE		
Vibration sense UE		
Vibration sense LE		
Position sense UE		
Position sense LE		
*Lhermitte		
*Paraesthesiae UE		
*Paraesthesiae trunk		
*Paraesthesiae LE		

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = mild vibration or figure-writing decrease only in 1 or 2 limbs
	2a = mild decrease in touch or pain or position sense and/or moderate decrease in vibration in 1 or 2 limbs 2b = vibration or figure-writing decrease, alone or in 3 or 4 limbs
	3a = moderate decrease in touch or pain or position sense and/or essentially lost vibration in 1 or 2 limbs 3b = mild decrease in touch or pain and/or moderated decrease in all proprioceptive tests in 3 or 4 limbs
	4a = marked decrease in touch or pain or loss of proprioception, alone or combined in 1 or 2 limbs 4b = moderate decrease in touch or pain and/or severe proprioceptive decrease in more than 2 limbs
	5a = loss (essentially) of sensation in 1 or 2 limbs 5b = moderate decrease in touch or pain and/or loss or proprioception for most of the body below the head
	6 = sensation essentially lost below the head

BOWEL/BLADDER FUNCTIONS

Definitions

***** = optional

BLADDER

Hesitancy/retention

0 = none
1 = mild, no major impact on lifestyle
2 = moderate, urine retention, frequent UTI
3 = severe, requires catheterisation
4 = loss of function, overflow incontinence

Urgency/incontinence

0 = none
1 = mild, no major impact on lifestyle
2 = moderate, rare incontinence, no more than once a week, must wear pads
3 = severe, frequent incontinence, several times a week up to once daily, must wear urinal
4 = loss of function, loss of bladder control

Catheterisation

0 = none
1 = intermittent, up to twice daily
2 = intermittent, > twice daily
3 = constant

Bowel

0 = none
1 = mild, no incontinence, no major impact on lifestyle, constipation
2 = moderate, must wear pads or alter lifestyle to be near lavatory
3 = severe, in need of intermittent enemata
4 = complete loss of function

***Sexual dysfunction**

0 = none
1 = mild
2 = moderate
3 = severe
4 = loss

BLADDER AND BOWEL FUNCTIONS	
Hesitancy/retention	
Urgency/incontinence	
Catheterisation	
Bowel dysfunction	
*Sexual dysfunction	

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = mild urinary hesitancy, urgency and/or constipation
	2 = moderate urinary hesitancy and/or urgency and/or rare incontinence and/or severe constipation
	3 = frequent urinary incontinence or intermittent self catheterisation once or twice a day, needs constantly enemata or manual measures to evacuate bowel
	4 = in need of almost constant catheterisation, intermittent self catheterisation more than twice a day
	5 = loss of bladder function, external or indwelling catheter
	6 = loss of bowel and bladder function

Definitions
The presence of depression and/or euphoria alone results in a score of 1 on the cerebral FS, but does not affect the EDSS score.

Depression/euphoria
0 = none
1 = present
Patient complains of depression or is considered depressed or euphoric by the investigator or «significant other».

Decrease in mentation
0 = none
1 = mild, difficulties apparent to patient and «significant other» such as impaired ability to follow a rapid course of association and of surveying complex matters, impaired judgement in certain demanding situations, able to handle the daily routine, but no tolerance for additional stressors, intermittently symptomatic to even normal levels of stress, reduced performance, tendency toward negligence due to obliviousness or fatigue.
However, not apparent while taking the history or performing the routine neurological examination.
2 = moderate, definite abnormalities on formal mental status testing, but still oriented to time, place and person
3 = marked, not oriented in 1 or 2 spheres of time, place or person, marked effect on lifestyle
4 = dementia, confusion and/or complete disorientation

Fatigue
0 = none
1 = present
Fatigue that interferes with daily activity will be scored with a maximum of 2 in the FS.

MENTAL STATUS EXAMINATION	
Depression	
Euphoria	
Decrease in mentation	
Fatigue	

FUNCTIONAL SYSTEM SCORE	
	0 = normal
	1 = mood alteration only (does not affect EDSS score)
	2 = mild decrease in mentation/fatigue
	3 = moderate decrease in mentation
	4 = marked decrease in mentation
	5 = dementia

AMBULATION

Definitions
Actual walking distance without assistance obligatory up to 500 m (if possible). Actual walking distance with assistance obligatory up to 150 m (if possible).

In the definitions of EDSS grades 6.0 and 6.5 both a description of assistance required and of the walking range are included. In general, the distinction of bilateral versus unilateral assistance required to walk overrules the walking range.
However, the following exceptions are suggested,
If a patient is able to walk considerably longer than 100 m (> 120) with two sticks, crutches or braces he is in grade 6.0.
If a patient is able to walk more than 10 m and less than 100 m with two sticks, crutches or braces he is in grade 6.5.
If a patient needs assistance by another person (as opposed to one stick, crutch or brace) and/or is not able to walk more than 50 m with one stick, crutch or brace he is in grade 6.5.

AMBULATION

Walking range as reported (without help or sticks)

meters

in min

Able to walk without rest or assistance

- > 100 meters, but < 200 meters
- > 200 meters, but < 300 meters
- > 300 meters, but < 500 meters
- > 500 meters
- Unrestricted

Actual distance (obligatory up to 500 m if possible)

meters

Unable to walk 100 m without constant assistance

Unilateral assistance meters

- Cane/crutch
- Other

Bilateral assistance meters

- Cane/crutch
- Other

Other person

SYNOPSIS OF FS SCORES

- Visual[1]
- Brainstem
- Pyramidal
- Cerebellar
- Sensory
- Bladder/Bowel[2]
- Mental

[1] For calculation of the EDSS the score of the visual FS is to be converted as follows, 6 = 4; 5 = 3; 4 = 3; 3 = 2; 2 = 2; 1 = 1.

[2] Scores 5 and 6 in the bowel/bladder FS are converted to 4 and 5 respectively.

KURTZKE EXPANDED DISABILITY SCALE (EDSS)

EDSS steps below 4 refer to patients who are fully ambulatory, and the precise step is defined by the functional systems (FS) score(s). EDSS steps between 4.0 and 5.0 are defined by both FS-scores and walking range. In general, the worst of both should determine the score. Steps 5.5-8.0 are exclusively defined by ability to ambulate or use wheelchair.

EDSS should not change by 1.0 step unless there is a change in same direction of at least one step in at least one FS.
EDSS should not be lower than each of FS (excepted visual and bowel/bladder FS).

0 normal neurological exam (all grade 0 in FS)

1.0 no disability, minimal signs in one FS1 (i.e. grade 1)

1.5 no disability, minimal signs in more than one FS1 (more than one grade 1)

2.0 minimal disability in one FS (one FS grade 2, others 0 or 1)

2.5 minimal disability in two FS (two FS grade 2, others 0 or 1)

3.0 moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory

3.5 fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)

4.0 ambulatory without aid or rest for > 500 m; up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps

4.5 ambulatory without aid or rest for > 300 m; up and about much of the day; characterised by relatively severe disability usually consisting of one FS grade 4 or combinations of lesser grades exceeding limits of previous steps

5.0 ambulatory without aid or rest for > 200 m (usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.5)

5.5 ambulatory without aid or rest > 100 m

6.0 unilateral assistance (cane or crutch) required to walk at least 100 m with or without resting

6.5 constant bilateral assistance (canes or crutches) required to walk at least 20 m without resting

7.0 unable to walk 20 m even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 h a day

7.5 unable to take more than a few steps; restricted to wheelchair; may need some help in transfer and in wheeling self

8.0 essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms

8.5 essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions

9.0 helpless bed patient; can communicate and eat

9.5 totally helpless bed patient; unable to communicate effectively or eat/swallow

10.0 death due to MS

Actual EDSS

Signature

[1] Mental function's grade 1 does not contribute to EDSS-step definitions

Patient's Name: _____ **Date:** _____/____/____
month day year

ID#: _____ **Test#:** **1 2 3 4**

MODIFIED FATIGUE IMPACT SCALE (MFIS)

Following is a list of statements that describe how fatigue may affect a person. Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. In medical conditions like MS, feelings of fatigue can occur more often and have a greater impact than usual. Please read each statement carefully, and then circle the one number that best indicates how often fatigue has affected you in this way during the past 4 weeks. (If you need help in marking your responses, tell the interviewer the number of the best response.) Please answer every question. If you are not sure which answer to select, please choose the one answer that comes closest to describing you. The interviewer can explain any words or phrases that you do not understand.

Because of my fatigue during the past 4 weeks....

		Never	Rarely	Sometimes	Often	Almost always
1.	**I have been less alert.**	**0**	**1**	**2**	**3**	**4**
2.	**I have had difficulty paying attention for long periods of time.**	**0**	**1**	**2**	**3**	**4**
3.	**I have been unable to think clearly.**	**0**	**1**	**2**	**3**	**4**
4.	**I have been clumsy and uncoordinated.**	**0**	**1**	**2**	**3**	**4**
5.	**I have been forgetful.**	**0**	**1**	**2**	**3**	**4**
6.	**I have had to pace myself in my physical activities.**	**0**	**1**	**2**	**3**	**4**
7.	**I have been less motivated to do anything that requires physical effort.**	**0**	**1**	**2**	**3**	**4**

Because of my fatigue
during the past 4 weeks....

		Never	Rarely	Sometimes	Often	Almost always
8.	**I have been less motivated to participate in social activities.**	**0**	**1**	**2**	**3**	**4**
9.	**I have been limited in my ability to do things away from home.**	**0**	**1**	**2**	**3**	**4**
10.	**I have had trouble maintaining physical effort for long periods.**	**0**	**1**	**2**	**3**	**4**
11.	**I have had difficulty making decisions.**	**0**	**1**	**2**	**3**	**4**
12.	**I have been less motivated to do anything that requires thinking.**	**0**	**1**	**2**	**3**	**4**
13.	**my muscles have felt weak.**	**0**	**1**	**2**	**3**	**4**
14.	**I have been physically uncomfortable.**	**0**	**1**	**2**	**3**	**4**
15.	**I have had trouble finishing tasks that require thinking.**	**0**	**1**	**2**	**3**	**4**
16.	**I have had difficulty organizing my thoughts when doing things at home or at work.**	**0**	**1**	**2**	**3**	**4**
17.	**I have been less able to complete tasks that require physical effort.**	**0**	**1**	**2**	**3**	**4**
18.	**my thinking has been slowed down.**	**0**	**1**	**2**	**3**	**4**
19.	**I have had trouble concentrating.**	**0**	**1**	**2**	**3**	**4**

Because of my fatigue during the past 4 weeks....

		Never	Rarely	Sometimes	Often	Almost always
20.	**I have limited my physical activities.**	**0**	**1**	**2**	**3**	**4**
21.	**I have needed to rest more often or for longer periods.**	**0**	**1**	**2**	**3**	**4**

Multiple Sclerosis Quality of Life

(MSQOL)-54 Instrument

For Further Information, Contact:

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INSTRUCTIONS:

This survey asks about your health and daily activities. Answer every question by circling the appropriate number (1, 2, 3, ...).

If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation in the margin.

Please feel free to ask someone to assist you if you need help reading or marking the form.

1. In general, would you say your health is:

(circle one number)

Excellent……1

Very good……..2

Good……..3

Fair…….……...4

Poor……5

2. **Compared to one year ago**, how would you rate your health in general **now**?

(circle one number)

Much better now than one year ago..... 1

Somewhat better now than one year ago…….2

About the same 3

Somewhat worse now than one year ago..... 4

Much worse now than one year ago 5

3-12. The following questions are about activities you might do during a typical day. Does **your health** limit you in these activities? If so, how much? (Circle 1, 2, or 3 on each line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not Limited at All
3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
5. Lifting or carrying groceries	1	2	3
6. Climbing several flights of stairs	1	2	3
7. Climbing one flight of stairs	1	2	3
8. Bending, kneeling, or stooping	1	2	3
9. Walking more than a mile	1	2	3
10. Walking several blocks	1	2	3
11. Walking one block	1	2	3
12. Bathing and dressing yourself	1	2	3

13-16. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Circle one number on each line)

	YES	NO
13. Cut down on the amount of time you could spend on work or other activities	1	2
14. Accomplished less than you would like	1	2
15. Were limited in the kind of work or other activities	1	2
16. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

17-19. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious).

(Circle one number on each line)

	YES	NO
17. Cut down on the amount of time you could spend on work or other activities	1	2
18. Accomplished less than you would like	1	2
19. Didn't do work or other activities as carefully as usual	1	2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(circle one number)

Not at all.....1

Slightly 2

Moderately.....3

Quite a bit 4

Extremely.....5

Pain

21. How much **bodily** pain have you had during the **past 4 weeks**?

(circle one number)

None 1

Very mild..... 2

Mild 3

Moderate..... 4

Severe 5

Very severe..... 6

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

(circle one number)

Not at all..... 1

A little bit 2

Moderately..... 3

Quite a bit 4

Extremely..... 5

23-32. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks...** (Circle one number on each line)

	All of the Time	Most Of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6
32. Did you feel rested on waking in the morning?	1	2	3	4	5	6

33. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

(circle one number)

All of the time.....1

Most of the time.....2

Some of the time 3

A little of the time.....4

None of the time.....5

Health in General

34-37. How TRUE or FALSE is each of the following statements for you.

(Circle one number on each line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
34. I seem to get sick a little easier than other people	1	2	3	4	5
35. I am as healthy as anybody I know	1	2	3	4	5
36. I expect my health to get worse	1	2	3	4	5
37. My health is excellent	1	2	3	4	5

Health Distress

How much of the time during the **past 4 weeks...**

(Circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
38. Were you discouraged by your health problems?	1	2	3	4	5	6
39. Were you frustrated about your health?	1	2	3	4	5	6
40. Was your health a worry in your life?	1	2	3	4	5	6
41. Did you feel weighed down by your health problems?	1	2	3	4	5	6

Cognitive Function

How much of the time during the **past 4 weeks...**

(Circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
42. Have you had difficulty concentrating and thinking?	1	2	3	4	5	6
43. Did you have trouble keeping your attention on an activity for long?	1	2	3	4	5	6
44. Have you had trouble with your memory?	1	2	3	4	5	6
45. Have others, such as family members or friends, noticed that you have trouble with your memory or problems with your concentration?	1	2	3	4	5	6

Sexual Function

46-50. The next set of questions are about your sexual function and your satisfaction with your sexual function. Please answer as accurately as possible about your function **during the last 4 weeks only.**

How much of a problem was each of the following for you **during the past 4 weeks?**

(Circle one number on each line)

MEN	Not a problem	A Little of a Problem	Somewhat of a Problem	Very Much a Problem
46. Lack of sexual interest	1	2	3	4
47. Difficulty getting or keeping an erection	1	2	3	4
48. Difficulty having orgasm	1	2	3	4
49. Ability to satisfy sexual partner	1	2	3	4

(Circle one number on each line)

WOMEN	Not a problem	A Little of a Problem	Somewhat of a Problem	Very Much a Problem
46. Lack of sexual interest	1	2	3	4
47. Inadequate lubrication	1	2	3	4
48. Difficulty having orgasm	1	2	3	4
49. Ability to satisfy sexual partner	1	2	3	4

50. Overall, how satisfied were you with your sexual function **during the past 4 weeks**?

(circle one number)

Very satisfied..... 1

Somewhat satisfied..... 2

Neither satisfied nor dissatisfied 3

Somewhat dissatisfied 4

Very dissatisfied..... 5

51. During the **past 4 weeks**, to what extent have problems with your bowel or bladder function interfered with your normal social activities with family, friends, neighbors, or groups?

(circle one number)

Not at all..... 1

Slightly..... 2

Moderately 3

Quite a bit..... 4

Extremely 5

52. During the **past 4 weeks**, how much did *pain* interfere with your enjoyment of life?

(circle one number)

Not at all..... 1

Slightly..... 2

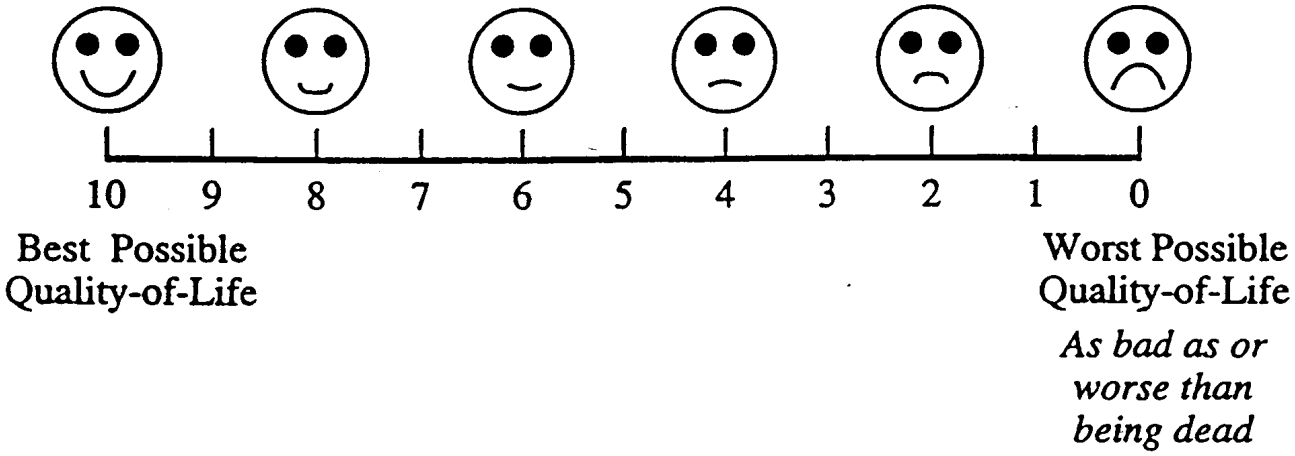
Moderately 3

Quite a bit..... 4

Extremely 5

53. Overall, how would you rate your own quality-of-life?

Circle one number on the scale below:



54. Which best describes how you feel about your life as a whole?

(circle one number)

Terrible 1

Unhappy 2

Mostly dissatisfied 3

Mixed - about equally satisfied and dissatisfied 4

Mostly satisfied 5

Pleased 6

Delighted 7

Scoring Forms for Multiple Sclerosis Quality of Life (MSQOL) -54

Table 1
MSQOL-54 Scoring Form

Table 2
MSQOL-54 Physical Health Composite Score

Table 3
MSQOL-54 Mental Health Composite Score

Table 1

MSQOL-54 Scoring Form

Scale/Item Number	Response 1	2	3	4	5	6		Subtotal	Final Score 0-100 point scale
Physical Health									
3.	0	50	100					_____	
4.	0	50	100					_____	
5.	0	50	100					_____	
6.	0	50	100					_____	
7.	0	50	100					_____	
8.	0	50	100					_____	
9.	0	50	100					_____	
10.	0	50	100					_____	
11.	0	50	100					_____	
12.	0	50	100					_____	
							Total:	_____ ÷ 10 =	_____
Role limitations due to physical problems									
13.	0	100						_____	
14.	0	100						_____	
15.	0	100						_____	
16.	0	100						_____	
							Total:	_____ ÷ 4 =	_____
Role limitations due to emotional problems									
17.	0	100						_____	
18.	0	100						_____	
19.	0	100						_____	
							Total:	_____ ÷ 3 =	_____
Pain									
21.	100	80	60	40	20	0		_____	
22.	100	75	50	25	0			_____	
52.	100	75	50	25	0			_____	
							Total:	_____ ÷ 3 =	_____
Emotional well-being									
24.	0	20	40	60	80	100		_____	
25.	0	20	40	60	80	100		_____	
26.	100	80	60	40	20	0		_____	
28.	0	20	40	60	80	100		_____	
30.	100	80	60	40	20	0		_____	
							Total:	_____ ÷ 5 =	_____
Energy									
23.	100	80	60	40	20	0		_____	
27.	100	80	60	40	20	0		_____	
29.	0	20	40	60	80	100		_____	
31.	0	20	40	60	80	100		_____	
32.	100	80	60	40	20	0		_____	
							Total:	_____ ÷ 5 =	_____

Table 1 (cont.) Scale/Item Number	Response 1	2	3	4	5	6	Subtotal	Final Score 0-100 point

Health Perceptions

1.	100	75	50	25	0		_____	
34.	0	25	50	75	100		_____	
35.	100	75	50	25	0		_____	
36.	0	25	50	75	100		_____	
37.	100	75	50	25	0		_____	
						Total:	_____ ÷ 5 =	_____

Social function

20.	100	75	50	25	0		_____	
33.	0	25	50	75	100		_____	
51.	100	75	50	25	0		_____	
						Total:	_____ ÷ 3 =	_____

Cognitive function

42.	0	20	40	60	80	100		_____	
43.	0	20	40	60	80	100		_____	
44.	0	20	40	60	80	100		_____	
45.	0	20	40	60	80	100		_____	
							Total:	_____ ÷ 4 =	_____

Health distress

38.	0	20	40	60	80	100		_____	
39.	0	20	40	60	80	100		_____	
40.	0	20	40	60	80	100		_____	
41.	0	20	40	60	80	100		_____	
							Total:	_____ ÷ 4 =	_____

Sexual function*

46.	100	66.7	33.3	0			_____	
47.	100	66.7	33.3	0			_____	
48.	100	66.7	33.3	0			_____	
49.	100	66.7	33.3	0			_____	
						Total:	_____ ÷ 4 =	_____

Change in health

2.	100	75	50	25	0			_____

Satisfaction with sexual function

50.	100	75	50	25	0			_____

Overall quality of life

	Response						
	1	**2**	**3**	**4**	**5**	**6**	**7**
53.	(multiply response by 10)						
54.	0	16.7	33.3	50	66.7	83.3	100

Total: _____ ÷ 2 = _____

Note: The total number of items in each scale is listed as the divisor for each subtotal. However, due to missing data, the divisor might actually be less than that if not every item within a given scale has been answered. For example, if item 38 in the Health Distress scale was left blank and the other 3 items in the scale were answered, then the "Total" score for Health Distress would be divided by '3' (instead of '4') to obtain the "Final Score."

* Males and females can be combined in the analysis even though question 47 is different for the two groups. The scale scores can also be reported separately for males and females.

Table 2
Formula for calculating MSQOL-54 Physical Health Composite Score

MSQOL-54 Scale	Final Scale Score	x	Weight	=	Subtotal
Physical function	_____	x	.17	=	_____(a)
Health perceptions	_____	x	.17	=	_____(b)
Energy/fatigue	_____	x	.12	=	_____(c)
Role limitations - physical	_____	x	.12	=	_____(d)
Pain	_____	x	.11	=	_____(e)
Sexual function	_____	x	.08	=	_____(f)
Social function	_____	x	.12	=	_____(g)
Health distress	_____	x	.11	=	_____(h)

PHYSICAL HEALTH COMPOSITE: Sum subtotals (a) through (h) = _____

Table 3
Formula for calculating MSQOL-54 Mental Health Composite Score

MSQOL-54 Scale	Final Scale Score	x	Weight	=	Subtotal
Health distress	_____	x	.14	=	_____(a)
Overall quality of life	_____	x	.18	=	_____(b)
Emotional well-being	_____	x	.29	=	_____(c)
Role limitations - emotional	_____	x	.24	=	_____(d)
Cognitive function	_____	x	.15	=	_____(e)

MENTAL HEALTH COMPOSITE: Sum subtotals (a) through (e) = _____

INFORMATION SHEET FOR PATIENTS

“Natalizumab versus interferon β-1b to prevent CDMS in patients with CIS and poor prognostic factors”

Multicenter study, double blind, randomized in 2 groups: one group will be treated with Natalizumab and the other with Interferon β-1b in patients with higher risk clinical isolated syndrome (CIS) to develop clinical definitive multiple sclerosis (CDMS).

Dear Patient,

You have been invited to participate in a research study of comparing 2 therapies in patients with clinical isolated syndrome (CIS).We are working to assess what therapy is most effective to prevent the development from CIS to CDMS. Before you decide whether to participate in the study or not, it is important that you read this Patient Information Sheet and ask the study doctor to explain anything you do not understand. This study has been approved by an ethics committee.

Purpose

The main purpose of the study is to see if natalizumab is more effective in the treatment of higher risk CIS compared to interferon β-1b . This study also attempts to determine whether treatment with natalizumab reduces the MRI lesion load, reduces the number of relapses by year and improve the aspects related to quality of life.

Treatment Groups

It is expected that about 172 patients are included in this study, approximately in 30 study centers.

There will be 2 treatment groups in the study, and compare the results of each treatment group to find out which treatment works best. To ensure that the treatment groups are similar, at baseline will assign you to a random group,

which means that neither you nor the study doctor can choose their treatment group. You have the same probability of being in each of the treatment groups.

To avoid that you know what treatment you are supplied, both groups will receive active treatment plus placebo. The placebo has the same appearance as the study drug but contains no active drug.

The treatment groups of this study are:

- Group 1: Nearly 86 patients. Natalizumab 300 mg infusion every 4 weeks plus placebo (sc) every-other day.
- Group 2: Nearly 86 patients. Interferon β-1b 0.25 mg (sc) every-other day plus placebo infusion every 4 weeks.

You will receive the study drug for up to 96 weeks (about 24 months). Neither you nor the study doctor or study staff will know if you are receiving natalizumab or interferon β-1b. However, in an emergency , we can figure out what treatment you are receiving .

Throughout the study, all SC injections (administered every other day) was placed on the center under supervision. His first SC injection will be administrated in the center. Then, it will be administrated by patients. At hospital you will learn how to do it.

The endovenous therapy will be administered at hospital every 4 weeks.

Visits to the center

During the study, you will come at hospital about 24 visits to our center for a period of about 24 months. The first visit will be a screening visit to see if you meet the conditions for participation in the study. If you meet the conditions for participation in the study, return to the center for a baseline visit in the next 4 weeks, after of additional tests you will be assigned to the treatment group and receive their first dose of study drugs. During the study , you will have visits

every 4 weeks. If you have symptoms of an MS relapse or making other significant changes in your health that may be related to use of the study drug, additional visits may be necessary to perform additional blood tests.

During the study the following tests shall be performed in some or all visits: Blood test, Magnetic resonance imaging brain scan, clinical evaluation and quality of life tests.

During the study you will be asked if you have had new symptoms of MS or if you will be experiencing worsening symptoms. Any side effects will be registered and if some of the laboratory tests show significantly abnormal results or other changes in your health, such as infection, your study treatment will be temporarily interrupted or permanently discontinued.

Interruption and withdrawal

You may decide to stop your study participation at any time. Before doing it, you should discuss your decision with the study doctor .

The treatment with the study drug will be interrupted if:

- you become pregnant
- you have symptoms of an allergic reaction to the study drug
- you show signs of impaired liver function
- you have a medical reason that necessitates stopping the study drug
- you not follow the rules of the study

The study doctor may decide to discontinue participation in this study at any time. Also withdraw your participation in this study for any of the following reasons: the study doctor decides that continuing is not best for you or that it is necessary for medical reasons you do not follow the rules of the study

If you need to interrupt the study drug permanently because of liver tests are abnormal, you are prompted blood and urine for safety analysis. Your doctor will

tell you the result of abnormal tests.

If you are removed from the study , you will be asked to return to the study center for follow-up visits.

Benefits

We hope that your participation in the study will be benefit. However, there is no guarantee that your MS better for their participation in this study. The results of the study can help in the future for people with a similar disorder.

Risks

If you think you are having an allergic reaction to medication (develops hives, difficulty breathing, swelling of the face, dizziness or other symptoms to explain the study staff) should contact the study doctor or seek medical attention immediately.

Risks of MRI

Rarely may cause a severe allergic reaction due to the use of radiological agent (gadolinium). The radiological agent may also cause you headaches, dizziness or fainting, brownout, nausea, vomiting, sweating, changes in the way things taste and symptoms at the injection site. Moreover, in patients with severely impaired renal function, some gadolinium contrast agents have been associated with a rare disorder, but serious and sometimes fatal (nephrogenic systemic fibrosis). If you have experienced any of these symptoms prior to a radiological agent, report it to the study doctor.

Risks of Natalizumab

The most common adverse reactions (incidence ≥ 10%) is headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea and rash.

Serious side effects

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML), an opportunistic viral

infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability, has occurred in patients who have received natalizumab.

Three factors that are known to increase the risk of PML in natalizumab-treated patients have been identified:

- Longer treatment duration, especially beyond 2 years. There is limited experience in patients who have received more than 6 years of natalizumab treatment.
- Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil).
- The presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk for developing PML.

These factors will be considered in the context of expected benefit when initiating and continuing treatment with natalizumab. Only the patients with low risk to develop LMP will be included in the study.

Herpes encephalitis and meningitis

Tysabri increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses. If it occurs, this treatment should be discontinued and appropriate treatment for herpes encephalitis or meningitis will be administered.

Hypersensitivity and antibody formation

Hypersensitivity reactions have occurred in patients receiving natalizumab, including serious systemic reactions at an incidence of <1%. These reactions usually occur within two hours of the start of the infusion. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnoea and chest pain. Generally, these reactions are associated with antibodies to natalizumab. Antibodies may be detected and confirmed with sequential serum antibody tests. The treatment will be discontinued if hypersensitivity reaction or antibody formation is detected.

Laboratory test abnormalities

Natalizumab may induce reduction in circulating lymphocytes, monocytes, eosinophils, basophils and nucleated red blood cells. Changes persist during treatment period but return to baseline levels usually within 16 weeks after the last dose.

Hepatotoxicity

Clinically significant liver injury, including acute liver failure requiring transplant, has been reported in patients treated with natalizumab. The treatment will be discontinued in patients with evidence of significant liver injury.

Risks of Interferon β-1b

The most common adverse reaction (incidence ≥ 5%) are: injection site reaction, lymphopenia, flu-like symptoms, myalgia, leukopenia, neutropenia, increased liver enzymes, headache, hypertonia, pain, rash, insomnia, abdominal pain, and asthenia.

Serious side effects

Anaphylaxis

Anaphylaxis has been reported as a rare complication of interferon β-1b use but if it occurs, the treatment will be discontinued.

Depression and suicide

Depression and suicide have been reported to occur with increased frequency in patients receiving interferon beta products. If a patient develops depression, discontinuation of the therapy should be considered.

Injection site necrosis

Typically, injection site necrosis occurs within the first 4 months of therapy. The necrotic lesions are usually 3 cm and rarely larger areas are affected. The treatment will be discontinued if multiple lesions occurs.

Flu-like symptom complex

It is one of the most common side effect among patients using Extavia but the incidence decreases over treatment period. Normally the median duration is 7 days. Analgesics and antipyretics on treatment days may help flu-like symptoms.

Compensation for damages

It has taken out an insurance, covering all patients participating in this study according to the Spanish Royal Decree 223/2004 of 6 February. This insurance will cover you if you suffer damages related to the study.

You must tell the study doctor immediately if you believe you have suffered damages for participating in this study. Insurance does not cover the normal progression of their disease or any damage, injury or complication due to a medical condition preexisting. If you have damages related to the study, the doctor will decide what medical care you need.

Confidentiality notice

Your medical information and any information obtained about you during this study will be kept confidential in accordance with the Organic Law 15/1999 on Protection of Personal Data and the corresponding Royal Decree 1720/2007 and not will be made public.

INFORMED CONSENT FOR PATIENTS

“Natalizumab versus interferon β-1b to prevent CDMS in patients with CIS and poor prognostic factors”

Multicenter study, double blind, randomized in 2 groups: one group will be treated with Natalizumab and the other with Interferon β-1b in patients with higher risk clnical isolated syndrome (CIS) to develop clinical definitive multiple sclerosis (CDMS).

Name of the patient:_____ Date of birth:_____

- I have read this Informed Consent Form or someone has read to me. It is written in a language that I understand.
- I understand what I was asked to do during this study and I have had time to think about what the study means for me.
- I have discussed this with the doctor / study personnel; I asked questions about the study and they have been answered satisfactorily.
- I have received enough information about the study
- I told the person obtaining consent if I am involved in other medical research studies.
- I have talked to ..... (name of the investigator 's / person obtaining informed consent)
- I understand I have to decide if I want to participate in the study and can later change my mind, and I can withdraw from the study at any time, without giving explanations.
- I understand that whatever I decide, my care and my legal rights are not affected.
- I understand that I can save a copy of the Patient Information Sheet and Informed Consent Form.
- Voluntarily, I agree to participate in this research study.

Signed and dated by the patient or the patient's legal representative:

Signature:_____ **Date:**_____**Hour:**_____