COMBAT-MS (COMparison Between All immuno-Therapies for Multiple Sclerosis)

A prospective long-term cohort study of safety, efficacy and patient's satisfaction of MS disease modulatory treatments in relapsing-remitting multiple sclerosis

Study ID: COMBAT-MS

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Date of Protocol: 2018-05-25 Version 3

AGREEMENT ON THE PROTOCOL

The investigator agrees to conduct the study as outlined in this protocol in accordance with good clinical practice (ICH-GCP, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf) and in accordance with the Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (1). 2
The investigator agrees, by written consent to this protocol, to fully co-operate and allowing direct access to all documentation, including source data, by regulatory authorities.
Significant changes to the protocol will be done only after approval from the Swedish Medical Products Agency, with the only exception where the immediate safety of the research patient is concerned (LVFS2011:19).

Approved consent in writing:

Signature:  Date: 2018-05-28

Professor Fredrik Piehl, Sponsor
Coordinating Principal Investigator

Signature: _____ Date: _____

Local Principal Investigator

Abbreviation and Definition of Terms

ADA	Anti-drug antibodies
AE	Adverse event
ARR	Annualized relapse rate
ASC	Academic Specialist Centre, Stockholm County Council
bRTX	Biosimilar rituximab
CEL	Contrast-enhancing MRI lesions
CIS	Clinically isolated syndrome
CNS	Central Nervous System
CRF	Case record form
DMF	Dimethyl fumarate
DMT	Disease-modifying treatment
EDSS	Expanded Disability Status Scale
FGL	Fingolimod
FSMC	Fatigue Scale for Motor and Cognitive Functions
GA	Glatiramer Acetate
GCP	Good Clinical Practise
IFN	Interferon
IMSE	Immunomodulation and Multiple Sclerosis Epidemiology studies
KS	Karolinska Sjukhuset
MAb	Monoclonal Antibodies
MPA	Swedish Medical Products Agency
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSIS-29	MS impact scale-29
NAB	Neutralizing drug antibodies
NFL	Neurofilament Light chain
NA	Not Applicable
NTZ	Natalizumab

PML	Progressive multifocal leukoencephalopathy
PCORI	Patient-Centered Outcomes Research Institute (Washington DC)
PPMS	Primary Progressive MS
QoL	Quality of Life
RA	Rheumatoid Arthritis
RCT	Randomized controlled trial
RRMS	Relapsing-Remitting Multiple Sclerosis
RTX	Rituximab
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDMT	Symbol Digit Modalities Test
SEK	Swedish Krona
SLE	Systemic Lupus Erythematosus
SMSreg	Swedish MS registry
SPMS	Secondary Progressive MS
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSQM-9	Treatment Satisfaction Questionnaire 9

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Protocol Summary

1. Background and Rationale

1.1. Background

Multiple sclerosis (MS) is an inflammatory disorder of the central nervous system (CNS) with onset primarily in young adults (2). The disease likely involves autoimmune mechanisms towards antigens present in CNS myelin leading to demyelination and secondary axonal damage, in turn the basis for permanent neurological deficits. Isolated injuries on the myelin sheath may be reversible, which is not the case for axonal and neuronal damage (3).
In the majority of cases (80-90%) the disease starts with a relapsing-remitting (RRMS) course, but in most cases convert to a phase of continuous worsening, secondary progressive MS (SPMS), after a mean of about 15 years of disease (4). A proportion of patients displays a relatively benign disease course, but long-term follow-up studies indicate that this fraction is at most 10 – 15 % of the whole MS population (5). The most conspicuous accumulation of disability occurs during the SP phase, but already at the time of diagnosis many patients display debilitating neuropsychological symptoms, significantly reduced quality of life and work capacity (6).

Multiple disease modifying treatments (DMTs) have been approved for RRMS, all of which vary in efficacy, safety, tolerability, duration of effect and mode of administration. In contrast, no DMT has yet been approved for progressive MS. DMTs are generally divided into first-line and escalation agents depending on safety and efficacy data from two-year randomized controlled trials (RCTs), most of which have been placebo controlled. Efficacy data from RCTs of limited duration are difficult to extrapolate to the real world situation, as enrolled patients are not entirely representative of the general RRMS population and have different underlying risks of long-term disability. Notably, most RCTs have included mainly treatment naïve patients without significant co-morbidities, while many DMT decisions are made for patients with signs of breakthrough disease or who display reduced tolerability with first-line DMTs, or with certain co-morbidities. Furthermore, relapse rate, the primary outcome of most RRMS RCTs, is a weak predictor of long-term disability and quality of life (QoL) (7); the outcomes ranked highest amongst the patients and other stakeholders. Therefore, patients and clinicians are left to make important treatment decisions based on imperfect results from short term RCTs with limited generalizability to real-life situations.

The treatment landscape for MS has changed considerably in the last two decades. The first-line treatments have up to recently only included treatments that involve self-administered injections (interferons, IFN; glatiramer acetate, GA). IFNs often are associated with side effects such as flu-like reactions and injection site reactions and GA requires daily subcutaneous injections often giving rise to local irritation and lipoatrophy at injection sites. In RCTs IFN and GA have been shown to decrease the annualized relapse rate (ARR) with 30–40% and inflammatory magnetic resonance imaging (MRI) activity with 60–85% (8, 9). Injectable DMTs is a common first line choice for newly diagnosed MS patients, or even from the first clinical episode (clinically isolated syndrome, CIS) (10). Data from controlled studies indicate a positive effect on the rate of disability accumulation in the short-term and observational data from sources such as the Swedish MS registry (SMSreg) also indicate a positive effect on the long-term prognosis of the disease (11), even if contradictory results also have been produced, see e.g. (12).
Depending on the individual formulation, the DMT cost per patient and year is between 80 000 and 100 000 SEK.

The monoclonal antibody (MAb) natalizumab (NTZ, Tysabri®) was registered for the treatment of inflammatory active MS in 2006, based on two phase III RCTs. In AFFIRM NTZ was compared with placebo over two years in a largely treatment naïve population of RRMS patients (13). In SENTINEL NTZ was compared to placebo as add-on treatment in patients having a relapse on interferon-beta1a (14). Based on current evidence NTZ is considered to have higher efficacy and better tolerability than injectable platform therapies (13). It must, however, be administered via intravenous infusions every four weeks, which impose burdens for the health care system and restricts the freedom for the patients. The effect on the disease is estimated to about 70% reduction of relapse frequency and 90% reduction of MRI activity (13). According to presently used indications, NTZ is used mainly as a second-line therapy for patients not responding to first-line therapies, or as first-line in patients with very high disease activity. Cessation of NTZ therapy has been associated with a rebound in disease activity, with increased risks of sometimes severe relapses. About 2-4% of patients develops neutralizing drug antibodies (NAB), which has been associated with loss of therapeutic effect and increased relapse risk. Apart from economical reasons, the main reason not to use NTZ as a first-line therapy is the documented increased risk to develop a severe opportunistic infection caused by JC virus; progressive multifocal leukoencefalopathy (PML). The frequency of PML in NTZ-treated patients is estimated to be approximately 0.1-5‰ per year, depending on the profile of a set of risk factors for developing PML that now can be estimated on an individual basis. For safety reasons more frequent MRIs are recommended in patients with increased risk of PML. The drug cost of NTZ is about 200 000 SEK yearly and it demands resources for monthly infusions as well. The increased efficiency, however, appears to lead to health economic gains through improved working capacity (15, 16).

Fingolimod (FGL; Gilenya®) was approved for RRMS in 2011 (2010 in the US) based on three phase III RCTs; Freedoms I and II were two-year placebo-controlled and in Transforms one year of FGL was compared with i.m interferon-beta1a (17, 18) (19). Compared with placebo FGL reduced ARR with 50-60%, and the risk of disability progression with a third in Freedoms I (not significant in Freedoms II). Compared to interferon, FGL reduced ARR with 40%. Alike NTZ, FGL in Sweden has been used mostly in patients displaying insufficient effect on first line therapies. In addition, FGL has been a common choice for patients switching from NTZ due to positive serology for JC-virus, however, then incurring a significant risk of new relapses (20). The yearly cost per patient of FGL is 200 000 SEK.

During the last two years, two oral treatments and another intravenously administered treatment have become available for treatment of RRMS. Teriflunomide (Aubagio®) is the active metabolite of leflunomide, an oral treatment approved for rheumatoid arthritis (RA). It was approved based on two phase III RCTs in RRMS; Temso and Tower (21, 22). In both studies two doses of teriflunomide were compared to placebo. At the highest dose (14 mg QD) teriflunomide reduced the risk of confirmed disability progression compared to placebo, and the ARR with a little more than a third. Although generally well tolerated, teriflunomide carries risks of peripheral neuropathies and other potentially serious adverse events (SAE). It is also potentially teratogenic, which is a problem when treating fertile women. The yearly cost in Sweden is 90 000 SEK.
Dimethylfumarate (DMF; Tecfidera®) is an oral compound with BID dosing. It was approved for RRMS based on two phase III RCTs in RRMS; CONFIRM and DEFINE (23, 24). In both studies DMF with BID or TID dosing were compared to placebo. DEFINE also included a GA open label arm. In both studies ARR was reduced with about 50%. The risk of confirmed disability progression was reduced with a little more than a third in DEFINE, but was not significant in CONFIRM. DMF initially was perceived as having a beneficial adverse event (AE) profile, but since its launch several cases of PML has now been documented. In addition, gastrointestinal discomforts and facial flush lead to reduced tolerability. The cost of DMF on the Swedish market is 140 000 SEK annually.

The monoclonal antibody alemtuzumab (Lemtrada®) represents the first DMT with a remission-inducing profile, which makes continuous immune suppression unnecessary. A treatment cycle involves two courses of repeated infusions and has a potential to induce long-term remission of disease activity through long-term ablation of immune memory cells (25). It is, however, associated with a number of autoimmune AEs, some of which are serious and potentially life-threatening, and therefore requires a diligent follow-up protocol. Alemtuzumab was approved based on two phase III RCTs in RRMS; Care MS I and Care MS II, where alemtuzumab was compared to s.c interferon-beta-1a (25, 26). Due to the lack of double blinding FDA initially decided not to approve alemtuzumab on the US market, however, this decision was later reversed. The price for two courses of alemtuzumab amounts to approximately 500 000 SEK, but about 30% of patients require additional treatment cycles.
Daclizumab (Zinbryta®), a drug previously approved for limiting the risk of transplant rejections, was recently approved for RRMS (27). As daclizumab has been withdrawn from the market it will not be further considered here.
Recently, two additional DMTs have been approved for RRMS; ocrelizumab (Ocrevus®), which is a novel anti-CD20 recognizing biological drug, and cladribine (Mavenclad®), which is an oral purine analogue that selectively suppresses lymphocytes. Ocrelizumab is indicated for active RRMS and cladribine for RRMS patients with highly active disease.

The monoclonal antibody rituximab (RTX; Mabthera®) recognises the surface antigen CD20 on B-lymphocytes and induce cell mediated (ADCC) and complement mediated lysis of these cells (28). After administration the number of B-lymphocytes in peripheral blood usually are below detection limits for 6–9 months after which they gradually return to normal values. RTX has been successfully used in many autoimmune conditions and is approved for RA, B cell lymphoma and systemic vasculitis (29). In neurological diseases it is also used off-label for neuroimmunological conditions such as neuromyelitis optica, myasthenia gravis and immune-mediated neuropathies. RTX is generally well tolerated and has very few severe side effects. The most feared complication of immunosuppressive treatment in neurology is the development of PML (30). It is difficult to accurately assess the risk of developing PML as a consequence of RTX treatment when used in monotherapy in non-immune compromised patients such as MS. Previous cases have almost inevitably been associated with the combination of RTX treatment and an underlying disease that involve increased risk for PML (e.g. lymphoma, SLE) or a combination with other immunosuppressive therapies such as methotrexate or cytotoxic drugs. Attempts to estimate the risk conferred by RTX itself has led to the conclusion that there is no proven over-risk for serious infections including PML by this treatment (31). In RA patients treated with RTX the risk of PML is estimated to approximately 1/25 000 treated individuals (32), which is even less than the estimated risk of developing PML in NTZ-treated individuals testing negative for JCV antibodies. Furthermore, patients with RA that have developed PML have also received other immunosuppressive drugs in combination and are generally older and with more concomitant diseases than what is usually the case in MS. In conclusion, it is expected that the risk profile of RTX used as monotherapy is beneficial compared with most DMTs currently approved for MS.

RTX has been tested in a placebo-controlled phase II study for RRMS, Hermes (33). After two infusions of 1000 mg RTX there was a significant reduction of exacerbation rate of more than 50% and >90% reduction of new or contrast-enhancing MRI lesions (CEL) (33). Patients in the study were followed for 48 weeks, a time point at which there were no sign of resuming MRI activity. In addition, RTX has been tested in a two-year placebo-controlled phase II/III RCT study for PPMS, Olympus (34). Active drug was not associated with a decreased risk of disability progression as a whole, but was significant in younger patients with signs of active disease on MRI. More recently, a Swedish phase II trial demonstrated reduced subclinical inflammatory activity measured via MRI and CSF neurofilament light (NFL) concentration, when switching patients in a clinically stable

phase treated with injectables to RTX (35), at the same time as treatment satisfaction improved considerably (36). A retrospective Swedish comparative effectiveness observational study showed a 92% reduced risk for relapse when switching to RTX compared with switching to FGL in patients terminating NTZ because of positive JC virus serology (20). In another recent retrospective Swedish observational study comprising 822 patients with on average two years treatment duration the frequency of serious side effects were low and there were no life-threatening complications or side effects leading to any type of sequelae attributable to the RTX treatment (37). Notably, a lower than previously used dose of RTX, 500 mg as a single infusion every 6 months, was shown to be equally effective as 1000 mg with the same dosing interval. Potentially this may also further improve a previously beneficial AE profile, in addition to reducing costs. The yearly drug cost per patient for this low dose regimen of two annual infusions of 500 mg is 25 000 SEK.

As noted previously, NTZ is associated with a 60-70% risk of rebound disease activity 4-7 months after discontinuation (38). This rebound disease activity can be fatal and severely disabling. Severe rebounds have been reported with pregnancy discontinuation (39), making choosing to continue or discontinue NTZ in JCV Ab+ patients or in women desiring pregnancy a major clinical challenge in RRMS with highly active disease at treatment start (40). In contrast to other DMTs, only RTX has been documented to continue to control disease activity after discontinuation of NTZ. Thus, as mentioned above, an observational study of 256 patients switching from NTZ to either RTX or FGL due to JCV positivity at three large Swedish MS centers showed that the odds or hazard ratios for a clinical relapse, contrast enhancing MRI lesions and AEs with RTX compared to FGL were 0.09, 0.01 and 0.50 (after correction for baseline differences), respectively (20). Lacking a formal RCT for this clinical situation and based on these findings RTX should be considered the most effective DMT for patients going off NTZ.

Two other MAb directed at the CD20 epitope on B-lymphocytes are presently evaluated as a treatment for MS and both have shown excellent results in phase II trials (41, 42). The humanised MAb ocrelizumab is manufactured by the same company as RTX (Roche) and differs from RTX in being a humanized MAb and therefore can be assumed to be less immunogenic than the chimeric counterpart. The pharmacodynamic properties are otherwise more or less identical by effectively depleting peripheral blood lymphocytes, but with more weight towards ADCC than complement mediated lysis as compared with RTX. In two recently published phase III trials ocrelizumab displayed a superior efficacy to prevent both relapses and accumulated disability compared with s.c interferon beta1a (43). Ocrelizumab was initially investigated also in RA but this program was terminated by the producer because of a signal for an increase in serious infections when combined with Methotrexate (44).

There is no phase III study planned for RTX in RRMS by its manufacturer Roche. On the other hand, there is extensive experience in the world from treatment of autoimmune conditions with RTX that offers superior safety data compared with most DMTs approved for MS. The patent protection for RTX expired 2016 thwarting any commercial interests in performing additional trails needed to register RTX as a licensed MS medication. Therefore, studies have to rely on investigator-initiated trials. A randomised phase III trial comparing RTX with DMF in early MS has been initiated in Sweden (RIFUND-MS, EudraCT 2015-004116-38).

Because of the apparent unique combination of efficacy on MS disease activity, favourable safety profile and patient-friendly treatment regime, RTX has already gained a widespread use in MS in Sweden, despite not having a formal MS indication. In fact, it is now the single mostly used MS DMT, though with large regional differences. Alike all approved MS DMTs a fundamental objective is to provide data on efficacy and safety over longer

time periods. A structured follow-up of RTX outcomes in relation to other MS DMTs is therefore essential, which is the focus of the present study.

Findings from this study will provide important information necessary to do well based health care decisions for patients in various phases of disease, with different treatment experiences and health profiles. This study will provide effectiveness and safety analyses of RTX, a drug that is accessible worldwide, compared with current approved MS DMTs. Furthermore, it will report outcomes that matter to patients and stakeholders and thus have the potential to gather data that can be used to improve the care for RRMS patients worldwide.
We plan to perform analyses in two different settings. In a pure retrospective registry-based study we will include all patients nationwide fulfilling inclusion criteria based on available data in the MS registry. However, the MS registry does not have complete coverage for all parameters, which will impact negatively on the power and validity of findings. In addition, the quality of registered data is difficult to assess accurately. In particular, this is a problem with one of the most important outcome measures, the EDSS rating scale of disability accumulation, since it will make disability outcome comparisons less reliable. This will be assessed in the COMBAT-MS study in which registered data will be validated against medical records and structured prospective annual assessments will be performed, however, with a rigorous non-intervention design with regard to choice of MS DMT.

2. Objectives of the Study

The overarching goal of this study is to describe the effectiveness and safety of RTX in comparison to other commonly used approved DMTs in the largest real-world population-based structured prospective follow-up cohort of RRMS patients. The study will include both treatment naïve patients on their first DMT and patients that have switched from a previous first line DMT (escalation/second-line). In keeping with the non-interventional design and real-world setting, we are not primarily interested in hypothesis testing of whether RTX is superior or non-inferior to a specific alternative DMT. Our main focus is instead in presenting point estimates and confidence limits for the range of alternative treatments currently used in clinical practice, with a range of alternative outcome measures. Different anti-CD20 DMTs will be analysed both as a group and separately.

The three outcomes that were ranked highest by patients surveyed and our stakeholders when choosing a DMT were long-term disability, QoL and risk of serious life-ending or -altering AEs. How specific MS DMTs affect early accumulation of permanent disability, a strong predictor of long-term disability (45), and QoL particularly in comparison with other DMTs in real life populations is not known.

2.1 Primary Objective

The two co-primary objectives of this study are

1. To compare the long-term effectiveness for preventing disability and reduced QoL of RTX with the most commonly used escalation agents, DMF, NTZ and FGL, in RRMS patients who have experienced disease activity on first-line DMTs
2. To compare the long-term effectiveness for preventing disability and reduced QoL of RTX with IFN, GA, NTZ, FGL and DMF in treatment-naïve RRMS patients

2.2 Secondary Objectives

The secondary objectives of the study are

- To compare the long-term safety of RTX with the most commonly used escalation agents, DMF, NTZ and FGL, in RRMS patients who have experienced disease activity on first-line DMTs
- To compare the long-term safety of treatment with RTX with IFN, GA, NTZ, FGL and DMF in treatment-naïve RRMS patients
- To compare drug survival, as a compound measure of effectiveness, side-effects and patient satisfaction, between RTX and IFN, GA, FGL, DMF and NTZ
- To compare patient satisfaction, fatigue and health related quality of life between treatment with RTX and IFN, GA, FGL, DMF and NTZ
- To study the occurrence of anti-drug antibodies (ADA) against RTX and their effect on B-lymphocyte levels and treatment efficacy.
- To compare the effectiveness on preventing MRI CELs between treatment with RTX and IFN, GA, FGL, DMF and NTZ in first-line and second-line settings, respectively.

2.3 Tertiary Objectives

The tertiary objectives of the study are

- To make health economic assessments and compare cost-effectiveness between treatment with RTX and IFN, GA, FGL, DMF and NTZ
- To compare the effectiveness, safety and patient satisfaction of RTX with other less frequent DMTs (teriflunomide, alemtuzumab).
- To compare serum/plasma neurofilament light (NFL) levels in patients treated with RTX and IFN, GA, FGL, DMF and NTZ.

3. Outcome Definitions

3.1 Primary Outcomes

The primary endpoints in this study are:

- Proportion of patients with baseline EDSS ≤2.5 progressing to 12 months confirmed EDSS ≥3 over 3 years of follow up.
- Proportion of patients with baseline EDSS ≥2.5 experiencing 12 months confirmed EDSS change +1 point over 3 years of follow up.
- Change in MSIS-29 over 3 years of follow up (change from baseline; mean value ±SD).

End points will be tested in -First line RTX vs DMF/GA/IFN/NTZ/FGL and Second line/escalation (switching from DMF/GA/IFN) RTX vs NTZ/FGL/DMF.

3.2 Secondary Outcomes

Secondary analyses comprise comparisons between the different treatment regimens concerning:

- Rate of malignancy, cardiovascular disease, serious infections and all-cause mortality in populations on therapy and ever treated, respectively. Data on safety outcomes will be obtained through linkage to the national Cancer, Patient, Prescribed Drug, and Causes of Death registers.
- Annual relapse rate.
- Mean number of CELs on yearly MRI.
- Drug survival and reason to terminate treatment.
- Yearly increase in mean and median EDSS.
- Yearly proportion of patients with at least 1 step increase in EDSS.

- Evaluation of frequency, titre, kinetics and clinical relevance of anti-RTX ADA.
- Yearly proportion of patients with No Evidence of Disease Activity (NEDA) -2 (free of exacerbations, new/enlarged T2-lesions and occurrence of CEL) as well as NEDA-3 (NEDA-2 plus no worsening of EDSS from baseline).
- Mean levels of NFL in serum.
- Yearly brain atrophy rate measured as brain parenchymal fraction (BPF) for different DMTs in a sub-population of patients and in relation to baseline values.
- Estimation of total societal costs per year after initiating treatment.
- Evaluation of health related QoL, fatigue and patient satisfaction during the treatment.
- Evaluation of work ability.

4. Study Design

4.1 Description of Study Design

This is a prospective non-interventional prospective cohort study assessing the long-term safety and efficacy of RTX treatment in MS compared with other common MS DMTs regarding both clinical and radiological parameters in a real-life population of patients with MS.

Assessments of a range of parameters, presently performed on other MS drugs in Sweden as a follow up program (IMSE), will be performed annually. These include amongst others demographics for treated patients, relapse rate, MRI activity, previous drug history and reasons for discontinuation, as well as a panel of patient reported scales (Symbol Digit Modalities Test, SDMT; MS check scale; MS impact scale-29, MSIS-29 and EQ-5D). In addition to the IMSE protocol, also the FSMC and Treatment Satisfaction Questionnaire 9 (TSQM-9) will be assessed.
Safety will be evaluated through linkage to national health care registers, with analysis describing the total numbers of SAEs, regardless of suspected causal association to a specific drug, and sensitivity analysis comparing rates while on drug, and ever after being exposed to the drug. Data availability through registers is limited by the annual updates of the Patient and Cancer register, and administrative time for the register-holding authorities (The National Board of Health and Welfare, Statistics Sweden), which will not allow for real-time assessments or annual reports at specific time points. To supplement this system, we will also ensure real-time reporting of SUSARs, through the Neuroregister platform, and summarize such events in annual reports to the Medical Products Agency. The SUSAR collection is thus intended to fill the gap in real-time safety surveillance of RTX, but will not form the basis of any comparative analyses across therapies.

4.2 Justification of Study Design

RTX is an existing drug with widespread use in autoimmune disorders, which since 2008 has been used increasingly also for MS both within and outside of clinical trials. A compound with identical mode of action (ocrelizumab) will likely be registered for MS in the near future, but the extensive clinical experience with RTX still makes this drug an attractive alternative treatment option in MS. RTX is furthermore considerably cheaper than formally approved MS drugs. The Swedish law allows the use of drugs outside of its approval (off-label) in certain situations. In case of RTX in MS, with a much expanding and systematic use a more structured follow-up of safety and effects is clearly warranted. In addition, a phase III trial with RTX compared to DMF for early RRMS has now been started in Sweden (EudraCT 2015-004116-38). However, alike the situation for several

other recently approved MS DMTs, there is a scarcity of long-term outcomes in real life patient populations. Given the high degree of registration of MS DMTs and a panel of disease related assessments in the SMSreg we can capitalize on already accumulated data that combined with structured annual prospective follow-ups can provide validated long-term outcomes. The combination of retrospective validation of registered data and prospective follow-up in a non-interventional design appears the most adequate design for this purpose.

In keeping with the Good ReseArch for Comparative Effectiveness (GRACE) principles (http://www.pharmacoepi.org/pub/1c29f69f-2354-d714-5100-1ef2b0e9abd9), we will focus on a "new user design", while using multiple comparator groups, representing the range of alternative DMTs available in clinical practice. We have pre-specified the overall outline of outcome measures and analyses to be done, and will document any later changes, including data driven specifications of covariate selection, in an updated study protocol for transparency.

5. Study Visits

5.1 Assessments during the Study

The follow-up protocol will largely harmonize with the IMSE follow-up protocol that is applied on all new immunomodulatory drugs in Sweden since the approval of NTZ in 2006 (ethical review board in Stockholm Dnr 2006/845-31/1, subsequent DMTs 2011/641-31/4) according to the scheme below. To this follow up protocol two additional rating instruments have been added; the FSMC and the TSQ. Study visits will be performed once annually for effectiveness outcomes and twice annually for compliance assessments.

	TEST/CONTROL	PRE-TREATMENT (BASELINE)	EVERY 6 MONTH	YEARLY	REGISTER IN SMSreg (www.neuroreg.se)
CONTROLS SPECIFIC FOR RITUXIMAB					
1	**EVALUATING % AND ABSOLUTE COUNTS OF B-LYMPHOCYTES**	YES	BEFORE EACH INFUSION		YES
CONTROLS ALL THERAPIES					
2	**CBC INCL DIFF, s-IgG, LFT, TSH, eGFR**	YES	RTX, FGL, NTZ, DMF	IFN, GA	NO
3	**MRI**	YES		YES	YES
4	**EDSS**	YES		YES	YES
5	**SDMT**	YES		YES	YES
6	**MSIS-29**	YES		YES	YES
7	**TSQ**	YES (if 2nd line)		YES	YES
8	**FSMC**	YES		YES	YES
6	**EQ-5D**	YES		YES	YES
10	**"MS-CHECK SCALE"**	YES		YES	YES
11	**SIDE EFFECTS**	NO	MONITORED EVERY VISIT		YES
12	**Serum/plasma/blood sample for ADA, NFL**	YES		YES	YES

6 Study Population

6.1 Number and Selection of Subjects

Patients will be identified through the SMSreg. Inclusion into the COMBAT-MS study will be subject to written informed consent. Given the rigorous non-intervention design of the study and very limited study-specific procedures outside of clinical practise, we expect participation rates to be very high. Based on preliminary calculations from the SMSreg the projected number of participants will be 3700 patients, out of which at least 1000 are treated with RTX first or second-line. A vast majority will already have started MS DMT prior to inclusion into the study.

6.2 Eligibility Criteria

6.2.1 Inclusion Criteria

The study population consists of all patients with CIS/RRMS diagnosed with the 2010 revised McDonald criteria (46) who;

- Initiate a first MS DMT (treatment naïve), or

  Initiate a second ever DMT, of a different drug class than the first, regardless of time between drugs or reason for discontinuation ("switchers") from 1st Jan 2011 to 30th June 2019, and
- Are followed at any of the University clinics of Sweden, and
- Consent to participation in COMBAT-MS core, and
- Are expected to be capable to follow study assessments and have decision-making capacity, e.g. lucid and oriented x 4 as judged by the investigator; and
- Are aged ≥18 years and ≤ 75 years at the day of signing the informed consent for inclusion into the prospective study (i.e. no age limit for retrospective data), and
- In case of fertile women, have been given information on potential DMT-related teratogenic effects and what type of contraception is considered safe according to respective SmPC.

6.2.2 Exclusion Criteria

Patients who at inclusion have the following characteristics are excluded from study participation;

- progressive forms of MS at start of the inclusion therapy (first bullet above).
- other neurological or other conditions that may interfere with follow study assessments or decision-making capacity.
- subjects with conditions listed as contraindications to the use of medicinal products used in the trial, e.g. gadolinium used for MRI scans.
- ongoing participation in other trials with blinded study medication or that interfere with the study protocol.

6.2.3 Retrospective Review of Inclusion/Exclusion Criteria

Medical charts will be reviewed for all patients for whom inclusion and exclusion criteria are fulfilled based on available information in the MS registry. This will be done in order to validate, and in case of incomplete or discrepant information, update, curate and fill in gaps based on the information available in the medical charts.

The following information will be reviewed and verified:

- Disease Onset
- MS diagnostic criteria
- Disease course at start of therapy
- Start/end of first MS treatment
- Start/end of second MS treatment

If fulfilling inclusion and exclusion criteria, the completeness of the following items will be checked:

- Relapses within the first 2 years of start of treatment and up till inclusion
- Reason for terminating treatment

- EDSS ratings, where special focus will be made to assess if EDSS at baseline was ≤2.5 or ≥3. Missing EDSS information can be included if listed in medical charts or can be deduced from clinical status.
- MRI scans: total number of T2 and gadolinium-enhancing lesions as given in the original radiology report.
- If missing also MSIS-29, EQ5D, MS check scale, TSQ can be included if noted in medical charts.
- Dates and doses of RTX infusions, as well as all moderate to severe infusion-related AEs

7. Treatment within the Study

Given the non-interventional design of the study, the protocol does not impose any regulations as to the choice or administration of the studied DMTs. However, we expect that DMT administration to large degree will follow the respective SPCs and in the case of RTX recommendations by the Swedish MS Association (initial infusion with 1000 mg iv and thereafter 500–1000 mg iv every 6 months). Any deviations to the protocol will be recorded in the SMSreg.

8. Blinding within the Study

There will be no blinding for neither treating physician nor patient within the study.

9. Disease Activity within the Study

Exacerbations will be evaluated according to standard clinical care and treated with methylprednisolone as determined justified by the treating physician. EDSS assessment according to a study specific protocol (appendix) will be performed at yearly visits.

10. Definitions of Exacerbation

A confirmed relapse is defined as new onset of neurological symptoms with a duration of more than 24 hours compatible with MS and preceded by a period of stable clinical symptoms of at least 30 days that does not have a more likely alternative explanation. Aggravation of previous symptoms may be counted as exacerbation if they arise without factors that can trigger pseudo bouts and are accompanied with new objective findings (e.g. worsening of visual acuity in an eye with previous optic neuritis and also pain behind the eye). All suspected relapses will be adjudicated by the local site-PI.

11. Withdrawal Criteria and Early Termination

Individual subjects have the right to withdraw their consent to participate in COMBAT-MS, but will then be followed up in the nationwide registry based study according to normal clinical routines. The investigator also has the right to withdraw subjects from the study in the event of change in eligibility or other reasons.

12. Study Assessments

The structure and content of scheduled visits in the study is given in the chart under point 5.1.

At the annual effectiveness outcome assessments, a standardized EDSS will be performed (appendix) together with SDMT and EQ-5D. Patients will be encouraged and instructed how to fill in the remaining patient reported scales prior to the visit on line. In the case this has not been done or the patient opt not to do it on line, this will be done during the visit. The patient will be actively interrogated about any potential AEs that has occurred since the last visit or any other health related issue. Finally, a MRI investigation will be performed, preferably before the clinical visit. In order to standardize the collection of data a help document for the visit will be distributed to participating centers. A nurse visit will be performed approximately at 6 months from the effectiveness assessment in order to check on compliance and safety issues. This can be done by telephone if deemed more convenient for the patient.

13. Study Medication

13.1 Study Medications included in the Study

The following DMTs will be considered study drugs:
IFN (Avonex®, Betaferon®, Extavia®, Plegridy®, Rebif®)
GA (Copaxone®)
DMF (Tecfidera®)
Teriflunomide (Aubagio®)
FGL (Gilenya®)
NTZ (Tysabri®)
Alemtuzumab (Lemtrada®)
RTX (Mabthera®)
bRTX (Ritemvia®)
Ocrelizumab (Ocrevus®)
Cladribine (Mavenclad®)

13.2 Concomitant Medications and Non-Drug Therapies

The focus of COMBAT-MS is effectiveness outcomes. Co-morbidities or concomitant medications will not be registered in the present study protocol. However, through cross-linkage with national compulsory registries for in- and outpatient care and prescribed drugs such information will be retrieved for the final analysis. The linkage studies with national health care registries are subject to additional ethical approvals (EPN Stockholm 2017/700-31/4).

14. Safety Reporting

14.1 Definition of a Serious Adverse Event

An SAE is defined as any untoward medical occurrence or effect, that at any dose:

- Results in death
- Is life threatening
- Requires hospitalization or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or a birth defect
- Is another significant medical event

An AE necessitating hospitalisation meets the regulatory definition for "serious" if the inpatient hospital admission includes a minimum of an overnight stay in a health care facility. Any AE that does not meet one of the definitions of serious (e.g. an AE requiring an emergency room visit, outpatient surgery or requires urgent investigation) may be considered by the investigator to meet the "other significant medical event" criterion for

classification as a SAE. Examples include allergic bronchospasm, malignancies, convulsions and blood dyscrasias.

14.2 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAE

Relapses or symptoms associated to MS is not considered as an AE and should not be recorded as such irrespective of hospitalisation. Planned operations or examinations requiring hospitalisations are not considered as SAE, only complications associated with the procedures specific for the study are considered as AEs or SAEs.

14.3 Definition of a Serious Adverse Reaction (SAR)

A SAR is an SAE where the investigator judges that the AE is at least possibly related to the use of any of the investigational medicinal products listed under 13.1.

14.4 Definition of a suspected unexpected serious adverse reaction (SUSAR)

A suspected unexpected serious adverse reaction (SUSAR) is any unexpected serious adverse reaction that is considered related to the study drug that; results in death, is life threatening (i.e. the subject was at risk of death at the time of the event); requires hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect. Furthermore, it is not expected when compared with the Reference Safety Information (RSI) in the most recent version of the SmPC for the respective DMT (se appendix).

If updates of the SmPC as provided in the appendix (i.e. *the Sponsor's* choice of RSI for this trial) will occur in the future, these updates will be submitted to MPA as substantial amendment applications with a statement that future SUSAR reports will determine expectedness based on the updated RSI. Upon approval, the updated SmPC will be communicated to all site PIs.

14.5 Reporting of Adverse Events

Each site PI is responsible for collection of SARs (as defined in Section 14.3) and report these regularly to the Sponsor, whose responsibility it is to summarize all SARs occurring in the study and provide the MPA with annual reports summarizing all accumulated events, both as line listings of all SARs and as a table specifying frequencies for each study drug sorted by SOC/PT (system organ class/preferred term). This annual report will also contain SUSARS (see below) be distributed to all sites in the study.
For all suspected SUSARs, i.e. where the site PI cannot determine if the event qualifies as a SUSAR as defined in Section 14.4 or not, these should be reported in an expedited fashion to the Sponsor for adjudication. The Sponsor will determine if the event should be reported as a SUSAR. Fatal or life threatening events deemed as a SUSAR will be reported within 7 days after the Sponsor first became aware of the reaction. A SUSAR, which is not fatal or life threatening, will be reported by the Sponsor within 15 days after becoming aware of the reaction. SUSAR reports will be prepared in CIOMS format and sent to registrator@mpa.se for uploading into EudraVigilance database, clinical trials module. During the study, an annual safety report (DSUR) on safety issues occurring among the trial subjects will be sent to the MPA and the relevant ethics committee, with a summary of events, separating the expected SARs (see above) from the unexpected SUSARs, and as well as providing information on the benefit-risk assessment, if changed since the study was approved.

15. Data Analysis and Statistical Considerations

15.1 Sample Size Considerations

The calculated study population is 3700 individuals and prospective inclusion will continue until 30th June 2019 or when the study is fully recruited. There is already over 2000 patients registered in the SMSreg treated with RTX but data has been collected only semi-systematically according to the guidelines of the SMSreg. The minimal detectable difference between RTX and the comparator groups depend on the projected sample sizes, of which we are fairly certain given the substantial data already collected. For the primary effectiveness outcome, it also depends critically on the proportion with valid information on EDSS at baseline and evaluation visit which is currently available for just over half of the patients, but which we aim to improve, and will also further improve by using multiple imputation. Using the NTZ group (where we currently have the most data) as a benchmark, we can calculate predictions for the number of patients we will be able to include in analysis of EDSS change. Of patients currently enrolled who started NTZ and have at least 3 years of follow-up, ~60% remained on therapy at 3 years, ~70% of these had valid MSIS29 and ~40% had valid EDSS at both baseline and evaluation visit after 3 years. Censoring for reasons other than drug discontinuation (death, emigration) is rare enough that it can be disregarded. Thus, while safety outcomes, drug persistence, and reasons for discontinuing therapy can be assessed among all patients initiating therapy, the change in EDSS can only be assessed in ~25% of patients, and the change in MSIS29 in 40-45%. By increasing the data capture of EDSS, through abstraction of clinical documents, we hope to bring this number to ~50%, which would require valid EDSS data on baseline and evaluation visit for 80% of all patients who remain on therapy at three years. Dividing the group further by baseline disability (EDSS below or over 2.5) would roughly reduce the sample by half for each outcome. The resulting minimal detectable difference would then be -9%-+12% with current EDSS registration rates, and -7%-+10% with improved EDSS rates; MSIS change (mean 0.3, SD 0.7) +/-0.10; remaining on drug +/- 5%; rate of malignancies (based on Bahmanyar et al. (47) with 5/1000) HR 2.6 – 3.9.

15.2 Key Elements of Analysis Plan

During data collection, semi-annual data summaries will be made, describing the treated population regarding demographic data, collected efficacy data as well as reported side effects. These reports will be used in combination with ad hoc supporting analysis to identify bottlenecks and limitations in the data collection, and ensure a more complete data set.

Effectiveness of therapy will be assessed primarily at an evaluation point 3 years after treatment initiation, measured as proportions experiencing disease progression, and proportions who have discontinued therapy. Results represent patients remaining on therapy still after 3 years, and must be interpreted in light of the proportion who has discontinued therapy before this date. The reason for discontinuing therapy will be used as an additional (secondary) outcome measure. Patients who temporarily reach an EDSS of 3.0, but subsequently improve will not be considered as having reached the endpoint. Outcomes on RTX will be tested relative to comparator with drugs by line of therapy using multivariable regression. Choice of covariates will be guided by observed baseline characteristics, but will at least include sex, age, several baseline disease activity measures (other than EDSS), and background demographic factors. The proportion remaining on therapy at 3 years will be modelled in multivariable regression models as described above, but also studied continuously over time with Kaplan-Meier curves and multivariable Cox regression, with time since treatment start as time scale. As the main patient reported measure

of treatment effectiveness, we will analyze mean change in MSIS29 from treatment initiation to evaluation visit in linear regressions. The distribution of delta values is expected to approximately follow the normal distribution, but if skewness is detected confidence intervals will be calculated using empirical bootstrapping.

A major component in the proposed project is to increase the data capture of EDSS, where we currently have data on only about 50-70% of all visits, meaning that the expected proportion with EDSS data on both baseline and evaluation visit is only about 40-50%. In addition to improving the data quality, we have the possibility to use multiple imputation to fill out missing values for EDSS, since we have access to several other measures with higher data coverage, including MSIS29. This imputation may provide some additional power, but will also help to assess the potential for, and to avoid, selection bias associated with measured baseline characteristics.

Safety outcomes will analysed using linkage to relevant health registries and assessed in time-to-event analysis, with special consideration to the possibility for effect heterogeneity by time since treatment initiation. To take the potentially long latency of malignancies into account, overall and subtypes of malignancies will be analysed both in "ever treated"-analysis, including all follow-up after treatment initiation, and "on drug" where only follow-up time on active treatment is considered. Data will be presented as number of events, crude and age/sex-standardized incidence rates, and when sample size permits (5+ events in smallest strata), hazard ratios from multivariable Cox regressions adjusting for sex, age, year of treatment start, baseline disease history, and additional covariates based on comparison of baseline characteristics across treatment cohorts.

16. Study Administration

16.1 Definition of Source Data

The SMSreg in combination with the patients' medical chart will constitute the original data source. Note that this does not refer to the SMSreg as a quality registry, but the local database at each center (beslutsstöd), which is considered part of the medical records system. In both instances, information about who and when changes have been performed can be traced via electronic signatures that is retained in the system.

16.2 Quality Control and Monitoring

Each clinical site-PI agrees on performing the study-related tests according to the protocol and GCP standards. Local GCP certified staff will supervise data collection and entry of data into SMSreg. External monitoring with regular site visits (at least yearly) will be performed by GCP qualified staff of the IMSE study coordination office, representing the *Sponsor* of the trial and independent of the clinical site monitored. The monitoring will comprise verification and checking against source data of all informed consents and identity of study subjects, as well as sample checks of other types of data. Central monitoring of data quality entered into SMSreg will be performed regularly by a biostatistician in order to detect inconsistencies.

16.3 Quality Assurance

It is the investigator's responsibility to ensure compliance with GCP and all applicable regulatory requirements. Regulatory agencies may conduct a regulatory inspection of this

trial. Such audits/inspections can occur at any time during or after completion of the trial. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

16.4 Study Closure

The last study visit in COMBAT-MS will be performed by 1st July 2022, after which the database will be locked. Final analyses and interpretation will be completed by 1st Oct 2022, with the draft final research report submission to the funder PCORI 1st Dec 2022.

16.5 Records Retention

The source data of the study is the SMSreg where collected data will be stored indefinitely. Files with curated data will be stored in a secure database, with necessary backup files, for a minimum of ten years at the Karolinska Institutet to allow for easy and timely retrieval when needed and to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems and staff.

16.6 Case Report Forms

The SMSreg will serve as electronic CRF. All outcome data will be documented in this register ("beslutsstöd"), which is not considered a quality register, by each study team. SAEs will be reported separately on separate SAE forms stored at each study site after being reported to the *Sponsor*.

16.7 Rules for Completing CRFs

The study personnel must ensure that all information entered into the CRF is consistent with the source data. All test and questionnaire completed by the subjects in the study should be filed in the respective CRF.

16.8 Corrections to CRFs

Corrections are done by changing directly in the SMSreg. All changes are electronically traceable regarding when and by whom the change has been done.

16.9 CRF Flow

The study personnel are responsible to complete the CRF after each subject visit.

17. Data Management

Statistical analyses (see above) will be performed by *the Sponsor* or person having an ethical permission to perform analyses on the relevant data sets. *The Sponsor* should be notified and involved in the discussions regarding specific scientific projects related to the data collected within the framework of COMBAT-MS.

18. Finance and Insurance

The study has received full financing by a research contract with PCORI (Washington DC) and will be conducted completely independent of any commercial interests. The start date for the project is the 1st of November 2016.
Every subject participating in the study is covered by the patient national insurance ("Patientförsäkringen").

19. Publication Policy

Yearly reports of aggregated data will be produced by the study administrator at the Karolinska Institutet and distributed to all participating trial sites. Scientific publications will be performed when the trial has reached an amount of data that is deemed clinically and scientifically relevant as determined by the steering committee. Substudies of scientific value will be performed as relevant research questions that may be answered by the dataset will emerge.
In the event of a publication, the names of the authors and their order of appearance will most likely be as follows: Coordinating investigator as first or last author, other investigators according to scientific contribution. All persons designated as authors should qualify for authorship and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility or appropriate portions of the content. Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2 and 3. In addition, a study group designated "COMBAT-MS study group" with involved study personnel will appear on the author list.

Appendices

EDSS rating scale, and other rating scales

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